TRANSLATION STATEMENT

Study Title: 28-Day Repeated Dose Oral Toxicity Study of in Rats

Study Number: SR09244

I, the undersigned, hereby certify that this is a true and accurate translation from the original Japanese final report into English, which was reviewed properly.

Safety Research Institute for Chemical Compounds Co., Ltd.

Translated by:

Masao Sunaga June 7, 2012

Masao Sunaga, D.V.M., Study Director Date

FINAL REPORT

(Translation)

Study Title: 28-Day Repeated Dose Oral Toxicity Study of in Rats

Study Number: SR09244

Safety Research Institute for Chemical Compounds Co., Ltd.

STATEMENT

Study Title: 28-Day Repeated Dose Oral Toxicity Study of in Rats

Study Number: SR09244

1. This study was conducted in compliance with the following GLP standards: "On the Standard for the Test Facility Conducting Tests Concerning New Chemical Substances, etc.," Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau (PFSB), Ministry of Health, Labour and Welfare, Japan (MHLW), November 21, 2003; No. 3 of the Manufacturing Industries Bureau, Ministry of Economy, Trade and Industry, Japan (METI), November 17, 2003; and No. 031121004 of the Environmental Policy Bureau, Ministry of the Environment, Japan (MOE); and "Partial Amendment of 'On the Standard for the Test Facility Conducting Tests Concerning New Chemical Substances, etc.'," Notification No. 0704001 of the PFSB, MHLW, July 4, 2008; No. 2 of the Manufacturing Industries Bureau, METI, June 30, 2008; and No. 080704001 of the Environmental Policy Bureau, MOE. The test methods used in the study were in accordance with "On the Test Method Concerning New Chemical Substances, etc." (Notification No. 1121002 of the PFSB, MHLW, November 21, 2003; No. 2 of the Manufacturing Industries Bureau, METI, November 13, 2003; and No. 031121002 of the Environmental Policy Bureau, MOE); "Partial Amendment of 'On the Test Method Concerning New Chemical Substances, etc.'" (Notification No. 1120001 of the PFSB, MHLW, November 20, 2006; No. 2 of the Manufacturing Industries Bureau, METI, November 13, 2006; and No. 061120001 of the Environmental Policy Bureau, MOE); and OECD Guideline for the Testing of Chemicals; Repeated Dose 28-day Oral Toxicity Study in Rodents (407), October 3, 2008.

2. This study was conducted in compliance with the study protocol, and no environmental factors that might have affected the reliability of the test results were found.

Safety Research Institute for Chemical Compounds Co., Ltd.

Name and seal affixed in the original	August 11, 2010
Masao Sunaga, D.V.M., Study Director	Date

QUALITY ASSURANCE STATEMENT

Study Title: 28-Day Repeated Dose Oral Toxicity Study of in Rats

Study Number: SR09244

This study was inspected by the Quality Assurance Unit of Safety Research Institute for Chemical Compounds Co., Ltd., as follows:

Phase of study inspection	Date of inspection	Date of report to Study Director	Date of report to Management
Study protocol	April 6, 2010	April 6, 2010	April 6, 2010
Study protocol amendment (No. 1)	April 23, 2010	April 22, 2010	April 23, 2010
Study protocol amendment (No. 2)	June 29, 2010	June 29, 2010	June 29, 2010
Receipt, labeling, and storage of the test substance	April 6, 2010	April 6, 2010	April 6, 2010
Preparation of test solutions	April 9, 2010	April 9, 2010	April 9, 2010
Receipt, quarantine, and acclimatization of animals	April 7, 2010	April 7, 2010	April 7, 2010
Group assignment	April 12, 2010	April 12, 2010	April 12, 2010
Administration	April 14, 2010	April 14, 2010	April 14, 2010
Observation of general appearance	April 14, 2010	April 14, 2010	April 14, 2010
Body weight measurement	April 14, 2010	April 14, 2010	April 14, 2010
Measurement of food consumption	April 14, 2010	April 14, 2010	April 14, 2010
Detailed clinical observation	April 20, 2010	April 20, 2010	April 20, 2010
Urinalysis	May 10, 2010	May 10, 2010	May 10, 2010
Functional test	May 7, 2010	May 7, 2010	May 7, 2010
Autopsy and organ weights	May 12, 2010	May 12, 2010	May 12, 2010
Hematological examination	May 12, 2010	May 12, 2010	May 12, 2010
Biochemical examination	May 14, 2010	May 14, 2010	May 14, 2010
Histopathological examination (preparation of specimens)	May 19, 2010	May 19, 2010	May 19, 2010
Histopathological examination (microscopy)	June 2, 2010	June 2, 2010	June 2, 2010
Raw data	July 26, 2010	July 26, 2010	July 26, 2010
Final report (draft): Tables and Figures	July 26, 2010	July 26, 2010	July 26, 2010
Final report (draft): Text	July 26, 2010	July 26, 2010	July 26, 2010
Final report	August 11, 2010	August 11, 2010	August 11, 2010

1. This study was conducted in compliance with "On the Standard for the Test Facility Conducting Tests Concerning New Chemical Substances, etc.," Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau (PFSB), Ministry of Health, Labour and Welfare, Japan (MHLW), November 21, 2003; No. 3 of the Manufacturing Industries Bureau, Ministry of Economy, Trade and Industry, Japan (METI), November 17, 2003; and No. 031121004 of the Environmental Policy Bureau, Ministry of the Environment, Japan (MOE); "Partial Amendment of 'On the Standard for the Test Facility Conducting Tests Concerning New Chemical Substances, etc.'," Notification No. 0704001 of the PFSB, MHLW, July 4, 2008; No. 2 of the Manufacturing Industries

Bureau, METI, June 30, 2008; and No. 080704001 of the Environmental Policy Bureau, MOE; "On the Test Method Concerning New Chemical Substances, etc." (Notification No. 1121002 of the PFSB, MHLW, November 21, 2003; No. 2 of the Manufacturing Industries Bureau, METI, November 13, 2003; and No. 031121002 of the Environmental Policy Bureau, MOE); "Partial Amendment of 'On the Test Method Concerning New Chemical Substances, etc.'" (Notification No. 1120001 of the PFSB, MHLW, November 20, 2006; No. 2 of the Manufacturing Industries Bureau, METI, November 13, 2006; and No. 061120001 of the Environmental Policy Bureau, MOE); and OECD Guideline for the Testing of Chemicals; Repeated Dose 28-day Oral Toxicity Study in Rodents (407), October 3, 2008.

2. The Quality Assurance Unit has reviewed the final report and determined the following: this study was conducted in compliance with the study protocol, the methods and procedures of this study were accurately described in this report, and the results presented in this report accurately reflect the raw data generated during this study.

Safety Research Institute for Chemical Compounds Co., Ltd.

Name and seal affixed in the original	August 11, 2010
Taku Katano, QA Representative	Date

TABLE OF CONTENTS

Study title: 28-day repeated dose oral toxicity study of in rats

Study number: SR09244

Purpose of the study: was orally administered to male and female rats for 28 days to investigate its toxicity and its profile, which was followed by a 14-day withdrawal after the end of dosing to evaluate recovery from toxicity detected.

Good Laboratory Practice standard and test guideline

Good Laboratory Practice (GLP) standard:

"On the Standard for the Test Facility Conducting Tests Concerning New Chemical Substances, etc.," Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau (PFSB), Ministry of Health, Labour and Welfare, Japan (MHLW), November 21, 2003; No. 3 of the Manufacturing Industries Bureau, Ministry of Economy, Trade and Industry, Japan (METI), November 17, 2003; and No. 031121004 of the Environmental Policy Bureau, Ministry of the Environment, Japan (MOE)

"Partial Amendment of 'On the Standard for the Test Facility Conducting Tests Concerning New Chemical Substances, etc.'," Notification No. 0704001 of the PFSB, MHLW, July 4, 2008; No. 2 of the Manufacturing Industries Bureau, METI, June 30, 2008; and No. 080704001 of the Environmental Policy Bureau, MOE

Test guidelines: "On the Test Method Concerning New Chemical Substances, etc." (Notification No. 1121002 of the PFSB, MHLW, November 21, 2003; No. 2 of the Manufacturing Industries Bureau, METI, November 13, 2003; and No. 031121002 of the Environmental Policy Bureau, MOE)

"Partial Amendment of 'On the Test Method Concerning New Chemical Substances, etc.'" (Notification No. 1120001 of the PFSB, MHLW, November 20, 2006; No. 2 of the Manufacturing Industries Bureau, METI, November 13, 2006; and No. 061120001 of the Environmental Policy Bureau, MOE)

OECD Guideline for the Testing of Chemicals; Repeated Dose 28-day Oral Toxicity Study in Rodents (407), October 3, 2008

Animal protection

This study was conducted in compliance with the Standard Operating Procedure (SOP/APW/001: Ethical Code for Animal Experimentation).

Regulation and standards:

"Act on Welfare and Management of Animals" (Act No. 105, October 1, 1973; Final Amendment, Act No. 50, June 2, 2006)

"Standards Relating to the Care, Management and Refinement of Laboratory Animals" (Notification No. 88 of the Ministry of the

Environment, Japan, April 28, 2006)

"Guidelines for Animal Experimentation" (Japanese Association for Laboratory Animal Science, approved on May 22, 1987)

Study sponsor

Name:
Address:
Study monitor:

Test facility

Name:	Safety Research Institute for Chemical Compounds Co., Ltd.
Address:	363-24 Shin-ei, Kiyota-ku, Sapporo 004-0839, Japan
Management:	Masao Kiguchi

Study Director

Name:	Masao Sunaga, D.V.M.
Affiliation:	Safety Research Division, Safety Research Institute for Chemical Compounds Co., Ltd.

Study personnel

Test substance management:
Shiho Kodama (responsible person),
Misako Ohkubo, and Mai Hirakata

Chemical analysis: Kenji Miya (responsible person, Nisso Chemical Analysis Service Co., Ltd.),
Shinpei Tushima, and Junko Tashiro (Nisso Chemical Analysis Service Co., Ltd.)

Animal husbandry: Teruhito Hirata (responsible person)

Quarantine and acclimatization:
Miyuki Kasahara, Takuya kajiwara, Hiromi Nozaki,
Hiromi Makino, Sachie Mizugami, and Ayako Yoshida

Administration, observation and measurement
Miyuki Kasahara, Takuya Kajiwara, Miyuki Kamijima, Hiromi Nozaki, Hiromi Makino, Sachie Mizugami, and Ayako Yoshida

Clinical laboratory tests:
Mariko Hirata (responsible person),
Saori Imamoto, Miyuki Kasahara, Takuya Kajiwara, Mitsue Katayama, Takuo Nakayama, Hiromi Nozaki, Masatoshi Furukawa, and Hitomi Yonezawa

Pathological examination:
Masatoshi Furukawa (responsible person),

Kohta Ito, Miyuki Kasahara, Chiaki Takahashi, Keiko Furukawa,
Takeshi Yamauchi, and Ryo Yokotani

Testing period

Study initiation:	April 6, 2010
Receipt of the test substance:	January 18, 2010
Receipt of animals:	April 7, 2010
Start of experiment:	April 14, 2010
Start of administration:	April 14, 2010
End of administration:	May 11, 2010
Autopsy at the end of administration:	May 12, 2010
Autopsy at the end of recovery:	May 26, 2010
Experiment completion:	June 30, 2010
Study completion:	August 11, 2010

SUMMARY

was orally administered at doses of 0 (control), 30, 100, and 300 mg/kg in male and female Jcl:SD rats (6 animals/sex/group) for 28 days to assess the potential toxicity and its profile. Recovery from toxicity was also investigated by continuous observation following withdrawal in recovery groups (6 animals/sex/group) at 0 and 300 mg/kg for 14 days from the day after the end of dosing.

1. In general appearance, tremor, staggering gait, jumping in cages, or tachypnea were noted in males and females in the 300 mg/kg group during dosing period from Day 1 of dosing.
2. In detailed clinical observation, relatively continuous tremor was sporadically noted only in the 4 limbs in the 300 mg/kg group.
3. In functional observation, abnormal righting reflex in air was observed in males and females in the 300 mg/kg group, with statistically significant differences in males. In addition, some males were hypersensitive to auditory stimulus, and males and females showed low or high grip strength, and significantly low motor activity counts or its tendency to be low in the 300 mg/kg group.
4. Food consumption was significantly and transiently low on Day 4 of dosing, and was higher than in the control group at the later stage of the dosing period with significant difference on Day 28 of dosing in males and females in the 300 mg/kg group. Body weight on Day 28 of dosing, body weight gain and percent body weight gain during the dosing period were significantly high in males in the 100 mg/kg group.
5. Hematological examination revealed significant shortening of activated partial thromboplastin time in males and females, and significant shortening of prothrombin time and significantly high reticulocyte counts in males in the 300 mg/kg group.
6. In biochemical examination, ALT, alkaline phosphatase, A/G ratio, albumin fraction and inorganic phosphorus were significantly high and β globulin fraction, total cholesterol and triglyceride were significantly low in males in the 300 mg/kg group.
7. In organ weights, absolute and relative liver weights were significantly high or tended to be high in males in the groups of 100 mg/kg and higher doses and females in the 300 mg/kg group. Absolute and relative thyroid weights tended to be high or were significantly high in males and females in the 300 mg/kg group.
8. Histopathological examination revealed slight increase in extramedullary hematopoiesis in the spleen in males and females in the 300 mg/kg group.
9. The changes observed at the end of dosing period tended to recover.
10. No changes related to the test substance administration were noted in urinalysis or autopsy findings.

Based on these results, No-observed-effect level (NOEL) of was considered to be 30 mg/kg/day in males and 100 mg/kg/day in females under the conditions of the present study.

INTRODUCTION

was orally administered at doses of 0 (control), 30, 100, and 300 mg/kg in male and female Jcl:SD rats (6 animals/sex/group) for 28 days to assess the potential toxicity and tis profile. Recovery from toxicity was also investigated by continuous observation following withdrawal in recovery groups at 0 and 300 mg/kg (6 animals/sex/group) for 14 days from the day after the end of dosing.

MATEIALS AND METHODS

1. Test substance

Name:
Abbreviation:
CAS No.:
Reference Number in Gazetted List in Japan:

Rational formula (structural formula):

Molecular weight:
Physicochemical properties:
Appearance;

Lot No.:	
Supplier:	Study sponsor
Amount obtained:	2 containers (NET 1000 g and 1090 g, shared with related tests)

Stability:
After completion of test operation, the analysis results of the test substance were obtained and stability was confirmed (Appendix 1-2).

Storage conditions:	Containers should be sealed and stored in an indoor well-ventilated place to avoid moisture absorption. Direct sunlight should be strictly prohibited (protected from light), attention should be paid for moisture and high

humidity.

Storage location: The refrigeration room in the test substance storage room (measured temperature: 2 to 8 °C)

Caution in handling: Sufficient ventilation should be provided in the work place. Adequate protection equipment such as protection glasses and gloves should be used. Washing hands and faces as well as gargle are required after handling the test substance. Care should be taken not to raise dust.

Sampling: Approximately 5 g of the test substance was collected as a sample and stored in the archives of the test facility.

Remaining test substance: After completion of administration and other test operation including that in the related tests, the remaining test substance was returned to the supplier.

2. Vehicle

Name: Purified water (Japanese Pharmacopoeia purified water)

Manufacturer: Yakuhan Pharmaceutical Co., Ltd.

Lot Nos.: 001076 and 001078

Expiration date: January 2013

Storage conditions: At room temperature

Caution in handling: Nothing specified.

3. Preparation of the test solutions and chemical analysis

Preparation method: On the basis that the concentration of the test substance was , the amount corresponding to 100% was accurately weighed out and diluted with the vehicle to obtain the required concentration. The mixture was homogenized using a stirrer to prepare the high-dose test solution.
The intermediate- and low-dose test solutions were prepared by diluting the high-dose test solution with the vehicle.

Preparation frequency: At least once every 8 days

Caution in preparation: The test substance was treated in a clean bench using masks, protection gloves and glasses, etc.

Storage conditions: Under refrigeration (measured temperature: 2 to 6 °C)

Stability of test solutions: The concentrations of in the 1 and 100 mg/mL preparations were measured immediately after the preparation, and after storage at room temperature for 4 h after under refrigeration for 10 days, which were confirmed to be stable (Appendix 2).
The preparation and analysis were conducted by Nisso

Chemical Analysis Service Co., Ltd.

Concentration confirmation of test solutions:

The concentrations of the test substance in the test solutions of all concentrations were analyzed twice in total, which were used at the first dosing and at the end of dosing period. The results showed that the concentrations of the 3, 10, and 30 mg/mL test solutions used at the first dosing and at the end of dosing period were 3.00 and 3.03, 10.5 and 10.1, and 30.3 and 29.8 mg/mL, respectively, which were confirmed to be appropriate (Appendix 2).

The preparation was performed by Safety Research Institute for Chemical Compounds Co., Ltd., and the analysis was performed by Nisso Chemical Analysis Service Co., Ltd.

Disposal of remaining test solutions:

The remaining test solutions were collected as industrial waste to be incinerated.

4. Test methods

4.1. Test system

Species, and strain:	Rat, Jcl:SD
Microbiological control:	SPF
Breeder:	Clea Japan, Inc.
Microbiological monitoring:	Data were obtained from the breeder.

Rationale for selection of test animal:

The animal species and strain were selected because rats are commonly used in toxicity studies, and the test facility has abundant experience of using the strain.

Number of animals ordered:	38 males and 38 females
Number of animals received:	40 males and 42 females
Age of animals at receipt:	Males and females; 4 weeks of age
Body weight standard at shipping:	Males: 50 to 110 g females: 50 to 100 g (representation by the breeder: males and females: 60 to 80 g)
Body weight range at receipt:	Males: 74 to 83 g females: 67 to 81 g

Age of animals at the start of administration:

Males and females: 5 weeks of age

Number of groups:	6 groups for each sex
Number of animals per group:	6 animals/sex/group

4.2. Quarantine and acclimatization

Method of quarantine: Animals were observed for general appearance once a day

and weighed at animal receipt, and at group assignment (2 days before administration). During the quarantine and acclimatization period, 1 female showed fracture of the upper incisor, but no abnormalities were noted in the other animals.

Period: For 5 days from Days 1 (day of receipt) to 6 of acclimatization in males and females

4.3. Group assignment

Based on the results of general appearance and body weights during the quarantine and acclimatization period, animals were selected for use in the study. Two days before the start of administration, 40 males and 41 females, excepting the female showing fracture of the upper incisor, were assigned to study groups by stratified random sampling so that group mean body weights during the quarantine and acclimatization period were comparable. Body weights of animals at group assignment ranged from 119 to 130 g in males and from 106 to 121 g in females, which were within ± 20% of the mean body weights (124.8 g in males and 114.1 g in females). Animals not selected were excluded from the study and treated according to the Standard Operating Procedure. Selected animals were observed for general appearance on the day before the start of administration.
Body weights at the start of dosing were 135 to 152 g in males and 107 to 139 g in females, and the mean body weights were 143.9 g in males and 125.9 g in females.

4.4. Identification of animals and cages

Animals: Animals were marked on the tail with an oil-based marker when received for individual identification before group assignment.
After group assignment, animal numbers were tattooed on the ear auricles for individual identification.

Cages: Before group assignment, a label indicating the study number and animal numbers at receipt, which was colored by sex, was attached to the front of each cage.
After group assignment, a label indicating the study number, study group, and animal number, which was colored by sex, was attached to the front of each cage.

4.5. Animal husbandry

4.5.1. Environmental conditions

Animal room number: No. 305
Temperature and humidity:
22 ± 3 °C (measured temperature: 21 to 25 °C), 50% ± 20% (measured humidity: 35% to 62%)
Ventilation frequency: 10 to 15 air changes/h

Lighting period: 12 h of artificial lighting (8:00 to 20:00)

4.5.2. Housing apparatus and method

Type of cage: Metal bracket cage (W 260 × D 380 × H 180, mm) with wire-mesh floor

Number of animals per cage: 2 or 3 during the quarantine and acclimatization period, and 1 after group assignment

Change of cages: At group assignment and once a week after group assignment, and every 2 weeks after that

Change of cage trays: Twice a week

Change of feeders: At the same time as changing cages

Flushing the pipes of the automatic watering system: Pipes of the automatic watering system were flushed with water once a week.

Water bottles: Water bottles were used only during urinalysis

Cleaning of the room: Once a day

Disinfection of the room: Once a day by swabbing using chlorine and iodine disinfectants, alternately every other week

4.5.3. Diet

Type and name: Pellet diet, CRF-1

Lot No.: 100203

Manufacturer: Oriental Yeast Co., Ltd.

Feeding method: Animals had free access to diet in metal feeders.

Analysis for contaminants and bacteria: The lot of diet used in the study was analyzed for contaminants or bacteria that might affect the study. The diet was analyzed by Eurofins Analytics K.K. for contaminants (No. AR-10-JP-000477-01) and by the diet manufacturer for bacteria (No. 10G03-027), and the analysis data of each lot were obtained from the diet manufacturer. The analyses revealed no deviations from the acceptable range in any parameters. The analytical parameters and their acceptable values were in accordance with those specified in the Standard Operating Procedure of Safety Research Institute for Chemical Compounds Co., Ltd.

4.5.4. Drinking water

Type: Sapporo City tap water

Method of supply: Animals had free access to drinking water using the

automatic watering system or water bottles.

Analysis for contaminants:

Water samples were collected from the end (animal room No. 301) of the piping system in the animal room used in this study on April 1 and July 1, 2010, and analyzed for contaminants that might affect the study. Analyses were performed by Nihon Eisei Co., Ltd. and the data were supplied (Nos. A220007 and A220982). The analyses revealed no deviations from the acceptable range in any parameters. The analytical parameters and their acceptable values were in accordance with those specified in the Standard Operating Procedure of Safety Research Institute for Chemical Compounds Co., Ltd.

4.6. Administration of the test substance

4.6.1. Dose selection

Doses: 0 (control), 30, 100, and 300 mg/kg

Rationale for dose selection:

In the preliminary study (SR09244P), the test substance dissolved in purified water was orally administered at doses of 0 (control), 10, 100, and 1000 mg/kg to SD rats [Jcl:SD], 3 males and 3 females/group, for 14 days. As the results, 1000 mg/kg was a lethal dose by a single dose, and 500 mg/kg, which was tested for exploration, was also a lethal dose. On the contrary, a possibility was suggested that 14-day repeated administration of the test substance at a dose of 100 mg/kg causes no effects. In the additional preliminary study (SR09244P2) in which the test substance was orally administered at 200 and 300 mg/kg for 14 days, enlarged liver accompanied with marked increase in the liver weight was noted in males and females in the groups of 200 mg/kg and higher, and a decrease in motor activity in males and staggering gait and tremor in males and females in the 300 mg/kg group. Based on these results and prolongation of the dosing period to 28 days, 100 mg/kg was selected as the intermediate dose, and 300 mg/kg and 30 mg/kg were selected as the high and low doses, respectively, by multiplying and dividing the intermediate dose by a common ratio of approximately 3. At the doses of 0 and 300 mg/kg, recovery groups were used to investigate recovery by 14-day withdrawal following 28-day

administration.

Composition of study groups:

Study group	Dose (mg/kg)	Concentration (mg/mL)	Number of animals (Animal No.)	
			Male	Female
<Toxicity study group>				
Control	0	0	6 (101 to 106)	6 (151 to 156)
Low dose	30	3	6 (201 to 206)	6 (251 to 256)
Intermediate dose	100	10	6 (301 to 306)	6 (351 to 356)
High dose	300	30	6 (401 to 406)	6 (451 to 456)
<Recovery study group>				
Control	0	0	6 (107 to 112)	6 (157 to 162)
High dose	300	30	6 (407 to 412)	6 (457 to 462)

Purified water was administered to the control group by the same method as in the other groups.

4.6.2. Administration

Administration method and route:

The test substance was orally administered by gavage into the stomach using a disposable gastric tube and a disposable syringe.

Rationale for selection of administration method, route and frequency:

In accordance with the test guideline.

Dosing frequency: Once daily, for consecutive 28 days

Dosing time: 9:00 to 12:00 except during urinalysis (during urinalysis: 11:30 to 12:00)

Dose volume: 10 mL/kg

Individual dose volume was calculated from body weight on the day nearest to the day of dosing.

4.7. Observation, measurement and examination

Observation, measurement and examination were conducted on the following parameters. The first day of dosing was defined as Day 1 of dosing, and the day after Day 28 of dosing as Day 1 of recovery.

4.7.1. Observation of general appearance

Animals observed: All animals

Period: From Day 1 of dosing to the day of autopsy (the days after Day 28 of dosing or Day 14 of recovery)

Frequency: Twice daily in the morning and afternoon. Once in the morning on the day of autopsy.

Observation method: Individual animals were observed for viability, appearance, behavior, and other changes. All abnormalities were recorded with the times of onset and disappearance.

4.7.2. Detailed clinical observation

Animals observed: All animals
Period: Before the start of dosing, on Days 7, 14, 21, and 28 of dosing and on Days 7 and 14 of recovery.
Observation method: Observation results were scored using predetermined scoring criteria, and the scores were recorded.
Observation parameters and methods:
a: Observed from outside of the cages: body position/posture, respiratory pattern, tremor/convulsion, stereotyped behavior (rolling/repetitive circling), and bizarre behavior (biting/selfmutilation)
b: Observed when animals were taken out of cages: Ease of removal, ease of handling, muscle tone, piloerection, condition of fur, appearance of the skin, eyes/eyeballs, and mucous membranes, pupil size, lacrimation, salivation, and other secretions or excretions.
c: Observed in an open field: gait, co-ordination of movement, reactivity to environmental stimuli, searching (sniffing and rearing), excretion (urination and defecation), stereotyped behavior (excessive grooming and unusual head movement), bizarre behavior (walking backward and vocalization), and aggression.

4.7.3. Functional test

Animals observed: All animals
Period: In Week 4 of dosing and in Week 2 of recovery
Observation and measurement methods
Observation results scored using predetermined scoring criteria or measured values by measurement equipment were recorded.
Observation and measurement parameters and methods:
a: Sensory and motor reactivity to the following stimuli: Examined on a workbench: visual, touch, auditory, pain, proprioceptive, and righting reflex stimuli.
b: Grip response:
Measured using CPU gage (Aikoh Engineering Co., Ltd.) 3 times each for the forelimbs and for the hindlimbs, and recorded as an integer in grams.
c: Motor activity:
Subsequent to the above *a* and *b*, measured using a measuring system (SUPERMEX and CompAct, Muromachi Kikai Co., Ltd.) for every 10 min for 1 h.

4.7.4. Body weight measurement

Animals weighed: All animals
Measurement days: Before dosing on Days 1, 4, 7, 14, 21, and 28 of dosing, on Days 7 and 14 of recovery, and the day of autopsy.
Measurement method:
Measured using an electronic balance (GX-2000, A & D Co. Ltd.) and recorded as an integer in grams.
Body weight gain and percent body weight gain:
Calculated using the following equations:

Dosing period

Body weight gain (g) =
Body weight (g) on Day 28 of dosing – Body weight (g) on Day 1 of dosing

$$\text{Percent body weight gain (\%)} = \frac{\text{Body weight gain (g)}}{\text{Body weight (g) on Day 1 of dosing}} \times 100$$

Recovery period

Body weight gain (g) =
Body weight (g) on Day 14 of recovery – Body weight (g) on Day 28 of dosing

$$\text{Percent body weight gain (\%)} = \frac{\text{Body weight gain (g)}}{\text{Body weight (g) on Day 28 of dosing}} \times 100$$

4.7.5. Food consumption

Animals measured: All animals
Measurement days: Before dosing on Days 1, 4, 7, 14, 21, and 28 of dosing, and on Days 7 and 14 of recovery
Measurement method: Measured using an electronic balance (GX-2000, A & D Co. Ltd.) and recorded as an integer in grams.
On the day before the start of administration, an adequate amount of diet was measured and set at each cage. The remaining amount and the amount supplied were measured on each measurement day. Only the remaining amount was measured on the day before the autopsy day.
Calculation of food consumption:
Calculated using the following equation:

Food consumption (g/rat/day) =

$$\frac{\text{Amount supplied (g/rat)} - \text{remaining amount (g/rat)}}{\text{Number of days between measurements (day)}}$$

4.7.6. Urinalysis

Animals examined: All animals
Time: Week 4 of administration and Week 2 of recovery
Method of urine collection:
Urine samples were collected from unfasted rats using metabolic cages for rats (KN-646, type B-1, Natsume

Seisakusyo Co., Ltd.). Urine samples collected from immediately after to approximately 3 h after dosing were used for the following parameters 1 to 8, and those collected for approximately 21 h for parameters 9 and 10. The urine samples were discarded after the completion of examination.

Examination parameters and methods:

1.	pH	Test paper method	SOP/CLN/105
2.	Protein	Test paper method	SOP/CLN/105
3.	Glucose	Test paper method	SOP/CLN/105
4.	Ketone body	Test paper method	SOP/CLN/105
5.	Urobilinogen	Test paper method	SOP/CLN/105
6.	Bilirubin	Test paper method	SOP/CLN/105
7.	Occult blood	Test paper method	SOP/CLN/105
8.	Color	Macroscopic observation	SOP/CLN/101
9.	Urine volume	Volumetric method	SOP/CLN/103
10.	Specific gravity	Refractometry	SOP/CLN/104

1 to 7: Multistix, Siemens Healthcare Diagnostics, K.K.
10: Refractometer, Uricon-S, Atago Co., Ltd.

4.7.7. Hematological examination

Animals examined: All animals
Time: Blood was collected at autopsy.
Examination method: Rats fasted overnight (for 17 to 23 h) were anesthetized with ether and blood was collected from the abdominal aorta. Approximately 1 mL of blood sample was treated with EDTA·2K (VENOJECT II vacuum blood collection tube, Terumo Corporation) and used for the following parameters 1 to 10. Another blood sample (approximately 1 to 2 mL) was treated with 3.8% sodium citrate and centrifuged at 3,500 rpm for 10 min to obtain plasma, which was used for the parameters 11 and 12. The blood and plasma samples were discarded after the completion of examination.
White blood cell specimens (May-Grünwald-Giemsa staining, SOP/CLN/205) were prepared and stored. As no abnormalities were found in distribution of white blood cells, the specimens were not microscopically examined.

Examination parameters and methods:

1.	Red blood cell count (RBC)	Electric resistance method	SOP/CLN/210
2.	Hematocrit (HCT)	Electric resistance method	SOP/CLN/210

3. Hemoglobin concentration (HGB)	SLS-hemoglobin method	SOP/CLN/210
4. Mean corpuscular volume (MCV)	Calculated from RBC and HCT	SOP/CLN/210
5. Mean corpuscular hemoglobin (MCH)	Calculated from RBC and HGB	SOP/CLN/210
6. Mean corpuscular hemoglobin concentration (MCHC)	Calculated from HCT and HGB	SOP/CLN/210
7. Reticulocyte count (Reticulocyte)	Flow cytometry method	SOP/CLN/210
8. Platelet count (Platelet)	Electric resistance method	SOP/CLN/210
9. White blood cell count (WBC)	Flow cytometry method	SOP/CLN/210
10. Differential count of WBC	Flow cytometry method	SOP/CLN/210
11. Prothrombin time (PT)	Thromboplastin method	SOP/CLN/208
12. Activated partial thromboplastin time (APTT)	Ellagic acid method	SOP/CLN/208

1 to 10: Automated hematology analyzer XT-2000 iV, Sysmex Co., Ltd.
11 and 12: Automated coagulometer KC4Δ, Trinity Biotech Plc.

4.7.8. Biochemical examination

Animals examined: All animals

Time: Blood was collected at autopsy.

Method of blood collection:

Rats fasted overnight (for 17 to 23 h) were anesthetized with ether and blood was collected from the abdominal aorta. The blood sample was treated with approximately 20 unit/mL of heparin sodium (Heparin sodium for injection N "Ajinomoto", 1,000 unit/mL, Ajinomoto Co., Inc.), which was centrifuged at 3,500 rpm for 10 min to obtain plasma. The plasma sample was used for the parameters 1 and 5. Another blood sample was collected into the tube containing separator (Sepaclen A, Eiken Kizai Co., Ltd.), which was centrifuged at 3,500 rpm for 10 min to obtain serum. The serum sample was used for the other parameters. After the end of examination, the plasma and serum samples were cryopreserved at −20 °C or under, and discarded on the day of study completion.

Examination parameters and methods:

1. Aspartate aminotransferase (AST)	JSCC method	SOP/CLN/402
2. Alanine aminotransferase (ALT)		

	JSCC method	SOP/CLN/402
3. Alkaline phosphatase (ALP)		
	JSCC method	SOP/CLN/402
4. γ-GTP	L-γ-glutamyl-3-carboxy-4-nitroanilide-substrate method	SOP/CLN/402
5. Glucose	Hexokinase method	SOP/CLN/403
6. Total cholesterol (T-Cho)	Enzyme method	SOP/CLN/403
7. Triglyceride (TG)	Removal of free glycerol method	SOP/CLN/403
8. Total bilirubin (T-Bil)	Azobilirubin method	SOP/CLN/404
9. Urea nitrogen (UN)	Urease-GLDH method	SOP/CLN/404
10. Creatinine (Crea)	Jaffé's method	SOP/CLN/404
11. Sodium (Na)	Ion selective electrode (ISE) method	SOP/CLN/406
12. Potassium (K)	Ion selective electrode (ISE) method	SOP/CLN/406
13. Chloride (Cl)	Ion selective electrode (ISE) method	SOP/CLN/406
14. Calcium (Ca)	OCPC method	SOP/CLN/406
15. Inorganic phosphorus (IP)		
	Fiske-Subba Row's method	SOP/CLN/406
16. Total protein (TP)	Biuret method	SOP/CLN/405
17. Protein fraction	Cellulose acetate membrane electrophoresis	SOP/CLN/427
18. Albumin/globulin ratio (A/G ratio)		
	Calculated from protein fraction	SOP/CLN/427
19. Albumin	Calculated from total protein and protein fraction	SOP/CLN/427

1 to 16: Automated clinical analyzer 7080, Hitachi High-Technologies Corporation

17 to 19: Automatic electrophoresis system AES320, Mishima Olympus, Co., Ltd.

4.7.9. Autopsy

Animals autopsied: All animals

Time: On the days after Day 28 of dosing or Day 14 of recovery

Method: Rats were observed for external appearance and blood was collected under ether anesthesia. They were then euthanized by exsanguination and macroscopically observed for all organs and tissues. The following organs and tissues were fixed and stored in 10% neutral buffered formalin. The eyeballs and harderian glands were fixed and stored in Davidson's fixative. The testes and epididymides were fixed in Bouin's solution and stored in 70% ethanol. The lungs were injected with a fixative and fixed by immersion in the fixative. Both sides of bilateral organs were fixed and stored in principle.

Organs and tissues: Brain (cerebrum, cerebellum and medulla oblongata), pituitary gland, spinal cord, thymus, thyroid, parathyroid, adrenals, spleen, heart, tongue, esophagus, stomach, liver, pancreas, duodenum, jejunum, ileum (including Peyer's patches), cecum, colon, rectum, mesenteric lymph nodes, submandibular lymph nodes, trachea, lungs, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicles (with coagulating glands), ovaries, uterus, vagina, eyeballs, harderian glands, femur (including bone marrow, right), sciatic nerve, and gross lesions (with a border with normal tissue)

4.7.10. Organ weight measurement

Animals weighed: All animals

Measurement days:

At autopsy

Measurement method:

The following organs were weighed using an electronic balance (ER-180A, A & D Co. Ltd.). Both sides of bilateral organs were weighed together.

Calculation of relative organ weights:

Relative weights were calculated using the following equation:

$$\text{Relative weight (\%)} = \frac{\text{Absolute weight (g)}}{\text{Body weight (g) on the day of autopsy}} \times 100$$

Organs: Brain, pituitary gland, thyroid, adrenals, spleen, heart, liver, kidneys, thymus, testes, epididymides, prostate, seminal vesicles (with coagulating glands), ovaries, and uterus

4.7.11. Histopathological examination

Animals examined: Specimens of all organs and tissues fixed and stored at autopsy were prepared, and those of all animals in the control and high dose groups were microscopically examined. The spleen showing changes which were likely to be effects of the test substance administration was microscopically examined in all males and females in the other group.
Gross lesions observed at autopsy were also examined microscopically.

Method: Organs and tissues were embedded in paraffin wax, sectioned and stained with hematoxylin and eosin and examined microscopically.
The parts with findings in the liver of 1 male (No. 409) in the

high dose group and 2 females (Nos. 156 and 160) in the control group were stained with Oil Red O stain and microscopically examined to detect triglyceride, which revealed positive results.

5. Statistical analyses

5.1. During dosing period, results in the toxicity study groups and those in the recovery study groups were totaled.

5.2. Means and standard deviations were calculated for the results of the following parameters: grip strength, motor activity, body weight, body weight gain and percent body weight gain, food consumption, urine volume, hematology, biochemistry, and absolute and relative organ weights, which were analyzed for homogeneity of variances by the Bartlett test. When an evidence of homogeneity of variances was indicated, the One way analysis of variance (ANOVA) was used, and when an evidence of heterogeneity of variances was indicated, the Kruskal-Wallis test was used. When ANOVA indicated a significant difference, Dunnett's test was used for comparison with the control group. When the Kruskal-Wallis test indicated a significant difference, the Mann-Whitney U-test was used for comparison with the control group.
The results of detailed clinical observation and functional observation, qualitative parameters of urinalysis, and urinary specific gravity were analyzed by the Kruskal-Wallis test, and when a significant difference was detected, the Mann-Whitney U-test was used for comparison with the control group.
Statistically significant level was set at 5% for comparison with the control group.

RESULTS

1. General appearance

The results of general appearance are shown in Tables 1 and 2 and INDIVIDUAL DATA 1-1-1 to 1-2-4.

[Dosing period]

In the 300 mg/kg group, tremor was noted in 4 males and 5 females on Day 1 of dosing, and staggering gait in 2 males and 2 females. These tended to occur continuously at the early stage of the dosing period, and intermittently at the later stage of the dosing period. Eight males and 5 females sporadically jumped in cages from Day 18 of dosing in males and from Day 21 of dosing in females. Tachypnea was once or twice noted in 2 males and 2 females.

No abnormalities were noted in males or females in the groups of 100 mg/kg or lower doses, except for scab formation at the right and left dorsal region noted in males in the 100 mg/kg group from Day 26 of dosing.

[Recovery period]

No abnormalities were noted in males or females in the 300 mg/kg or control group.

2. Detailed clinical observation

The results of detailed clinical observation are shown in Tables 3 to 8 and INDIVIDUAL DATA 2-1-1 to 4-14-2.

[Dosing period]

No significant differences were noted in any observation parameters at any observation time in males or females in the test substance groups compared to the control group. In the 300 mg/kg group, relatively continuous tremor was sporadically noted only in the 4 limbs. No other neurobehavioral abnormalities such as sedation, excitement, or bizarre behavior were noted.

[Recovery period]

No significant differences were noted in any observation parameters at any observation time in males or females in the 300 mg/kg group compared to the control group. No neurobehavioral abnormalities such as sedation, excitement, or bizarre behavior were noted.

3. Functional test

The results of functional test are shown in Tables 9 to 12 and INDIVIDUAL DATA 5-1-1 to 6-4-2.

[Week 4 of dosing]

In functional observation, abnormal righting reflex in air was noted in 6 males and 2 females in the 300 mg/kg group, with statistically significant differences in males. Three males were hypersensitive to auditory stimulus, which was not significant change. No significant differences were noted in any test parameters in males or females in the groups of 100 mg/kg or lower doses compared to the control group. Grip strength of the forelimbs in males in the 300 mg/kg group were significantly lower than in the control group, and that of the hindlimbs in females were significantly higher than in the control group. No significant differences were noted in males or females in the groups of 100 mg/kg or lower doses.

In the 300 mg/kg group, motor activity counts were significantly low at 20'–30' and 50'–60' after the start of measurement in males and the total counts tended to be low in males and females with no statistically significant differences. No similar tendency was demonstrated in males or females in the groups of 100 mg/kg or lower doses.

[Week 2 of recovery]

No significant differences were noted in functional observation, grip strength, or motor activity counts in males or females in the 300 mg/kg group compared to the control group.

4. Body weight

Body weight change is shown in Figures 1 and 2, Tables 13 and 14, and

INDIVIDUAL DATA 7-1-1 to 7-2-4.

[Dosing period]

In the 300 mg/kg group, no significant changes were noted in males or females compared to the control group.

In the 100 mg/kg group, body weight on Day 28 of dosing as well as body weight gain and percent body weight gain were significantly high in males. In the 30 mg/kg group, body weight from Day 14 of dosing to autopsy as well as body weight gain and percent body weight gain during dosing period were significantly low in females. These changes were not dose dependent, and were not considered toxicologically significant.

[Recovery period]

No significant changes were noted in males or females in the 300 mg/kg group compared to the control group.

5. Food consumption

Food consumption is shown in Figures 3 and 4, Tables 15 and 16, and INDIVIDUAL DATA 8-1-1 to 8-2-4.

[Dosing period]

In the 300 mg/kg group, food consumption was significantly and transiently lower than in the control group in both males and females on Day 4 of dosing, and was significantly high in males and females on Day 28 of dosing.

No significant changes were noted in males or females in the 100 mg/kg group.

In the 30 mg/kg group, food consumption was significantly low in females on Days 14 and 21 of dosing, which was not dose dependent. No significant changes were noted in males.

[Recovery period]

No significant changes were noted in males or females in the 300 mg/kg group compared to the control group.

6. Urinalysis

The results of urinalysis are shown in Tables 17 to 20, and INDIVIDUAL DATA 9-1-1 to 9-4-2.

[Week 4 of dosing]

No significant changes were noted in males or females in any test substance groups compared to the control group.

[Week 2 of recovery]

No significant changes were noted in males or females in the 300 mg/kg group compared to the control group.

7. Hematological examination

The results of hematological examination are shown in Tables 21 to 24, and INDIVIDUAL DATA 10-1-1 to 10-4-4.

[End of dosing period]

In the 300 mg/kg group, prothrombin time and activated partial thromboplastin time in males and activated partial thromboplastin time in females significantly shortened compared to the control group. Reticulocyte count and differential neutrophil count were significantly high in males.

In the 100 mg/kg group, differential neutrophil count was significantly high in males. No significant changes were noted in females.

In the 30 mg/kg group, activated partial thromboplastin time significantly shortened in females, which was not dose dependent. No significant changes were noted in males.

No dose-dependency was noted in the extent of the increases in differential neutrophil count in males in the 300 and 100 mg/kg groups and in white blood cell count in males in the 100 mg/kg group.

[End of recovery period]

Mean corpuscular hemoglobin concentration in males in the 300 mg/kg group was significantly lower than in the control group, which was considered not toxicologically significant because no changes were noted in the other erythrocyte parameters. No significant changes were noted in females.

8. Biochemical examination

The results of biochemical examination are shown in Tables 25 to 28, and INDIVIDUAL DATA 11-1-1 to 11-4-4.

[End of dosing period]

In the 300 mg/kg group, sodium and chloride were significantly low in males and females compared to the control group, and inorganic phosphorus was significantly high in males. In addition, ALT, alkaline phosphatase, A/G ratio, and albumin fraction were significantly high and total cholesterol, triglyceride, and β globulin fraction were significantly low in males.

In the 100 mg/kg group, sodium and chloride were significantly low in males, and triglyceride was significantly low in females.

In the 30 mg/kg group, triglyceride was significantly low in females. No significant changes were noted in males.

[End of recovery period]

In the 300 mg/kg group, total cholesterol was significantly high in males and females compared to the control group, and triglyceride was significantly high in males.

9. Autopsy

Autopsy findings are shown in Tables 29 and 30, and INDIVIDUAL DATA 12-1-1 to 12-4-2.

[End of dosing period]

In the 300 mg/kg group, fracture of the left upper incisor was noted in 1 female, and no changes related to the test substance administration were noted in males or females.

In the 100 mg/kg group, scab formation at the right and left dorsal skin was noted in 1 male, and no changes related to the test substance administration were noted in males or females.

In the 30 mg/kg and control groups, no abnormal findings were noted in males or females.

[End of recovery period]

In the 300 mg/kg group, caudal process of caudal lobe, and grayish white patches in the right and middle lobes were noted in 1 male. These changes were not considered related to the test substance administration because they histopathologically corresponded to slight periportal fatty change which was positive for oil red O staining, and the same change was histopathologically noted in 2 females in the control group at the end of dosing.

No abnormal findings were noted in females in the 300 mg/kg group or males or females in the control group.

10. Organ weights

Organ weights are shown in Tables 31 to 34, and INDIVIDUAL DATA 13-1-1 to 13-4-4.

[End of dosing period]

In the 300 mg/kg group, absolute and relative liver and spleen weights in males were significantly higher than in the control group, and liver weight tended to be high in females. Absolute and relative thyroid weights tended to be high in males and females, and the relative thyroid weight was statistically significantly high in males. In the 100 mg/kg group, absolute and relative liver and spleen weights were significantly high in males. No significant changes were noted in females. In males, absolute weight of seminal vesicle was significantly high, which was not dose dependent.

In the 30 mg/kg group, absolute and relative spleen weights were significantly high in males. In addition, relative epididymis weight was low in males and relative brain weight was significantly high in females, both of which were not dose dependent.

[End of recovery period]

In the 300 mg/kg group, relative liver weight was significantly high in males.

Absolute and relative heart weights were significantly high in males, which were not considered toxicologically significant because they were not noted at the end of dosing period and no abnormalities were histopathologically detected.

11. Histopathological examination

Histopathological findings are shown in Tables 35 and 36, and INDIVIDUAL DATA 14-1-1 to 14-4-2.

[End of dosing period]

Spleen: Slight increase in extramedullary hematopoiesis was noted in 4 males and 1 female in the 300 mg/kg group, but was not noted in the groups of 100 mg/kg or lower doses.

Other organs and tissues: No increases in the incidence or grade indicating effects of the test substance administration were noted in any organs or tissues of males or females in the control or 300 mg/kg group.

Macroscopically abnormal regions: At the site of fracture of the left upper incisor in 1 female in the 300 mg/kg group, moderate gingivitis was noted.
At the site of scab formation at the right and left dorsal skin in 1 male in the 100 mg/kg group, ulcer, scab, and cellular infiltration of inflammatory cells, fibrosis, and edema of the dermis were noted, all of which were slight in degree.

[End of recovery period]

Spleen: No abnormal findings were noted in males or females in the 300 mg/kg group.

Other organs and tissues: No increases in the incidence or grade indicating effects of the test substance administration were noted in any organs or tissues of males or females in the control or 300 mg/kg group.

DISCUSSION

was orally administered at doses of 0 (control), 30, 100, and 300 mg/kg in male and female Jcl:SD rats (6 animals/sex/group) for 28 days to assess the potential toxicity and tis profile. Changes indicative of the test substance administration included those in general appearance, detailed clinical observation, food consumption, liver, spleen, and thyroids.

In general appearance and detailed clinical observation, tremor, staggering gait, jumping in cages, or tachypnea were noted in males and females in the 300 mg/kg group during dosing period from Day 1 of dosing, which were considered related to the test substance administration. The test substance contains lithium, and in a previous study, a stereotyped behavior of repeatedly rubbing jaw on the floor of cage was reported in some rats treated with lithium bromide[1)]. Lithium salt (lithium carbonate) has been used

as the therapeutic agent for mania and manic state[2], and in addition to the neuromuscular changes such as tremor and ataxia of gait, changes in the central nervous, cardiovascular, and digestive systems, as well as renal disorder, etc. are known.[3] On these basis, tremor and jumping observed in the present study were considered to be associated with lithium contained in the test substance. The abnormal righting reflex in air and hypersensitivity to auditory stimulus (only males), low or high grip strength, significantly low motor activity counts or its tendency to be low noted in males and females in the 300 mg/kg group in the functional test were considered to be attributable to the comprehensive movement disorders caused by tremor and other findings in general appearance.

In biochemical examination, sodium and chloride were significantly low in males and females in the 300 mg/kg group and males in the 100 mg/kg group. These changes were considered related to the fact that the lithium ion equally behaves in the living body as sodium ion[1), 3)], and were considered to be a decrease in blood concentration of sodium ion, which synchronizing with excretion of lithium ion administered in a large amount. Thus, these were not considered indicative of onset of toxicity. In a similar manner, significantly low chloride value was considered to be accompanying the low sodium value, which was associated with the fact that chloride ion is excreted and reabsorbed with sodium ion.

Food consumption was significantly and transiently low on Day 4 of dosing, and was significantly high on Day 28 of dosing in males and females in the 300 mg/kg group. The transient decrease in food consumption was considered to be effects of taste of the test solution and other physical factors, because no effects were noted in body weight change. The high food consumption in males and females at the later stage of the dosing period indicated relation to the test substance administration, though its mechanism was not clarified, because body weight on Day 28 of dosing and body weight gain and percent body weight gain during the dosing period were significantly high in males.

Effects on the liver were observed as follows: absolute and relative liver weights tended to be high in males and females in the 300 mg/kg group and males in the 100 mg/kg group, which were statistically significant in males. In males in the 300 mg/kg group, ALT, alkaline phosphatase, A/G ratio, albumin fraction and inorganic phosphorus were significantly high and β globulin fraction was significantly low. Histopathological examination, however, revealed no clear changes in the liver which were related to the test substance administration in males or females. Therefore, these changes were not considered indicative of hepatic dysfunction, but raised a possibility that the weight increases and changes were related to enzyme induction caused by enhanced drug metabolism. The significant shortening of activated partial thromboplastin time in males and females in the 300 mg/kg group and prothrombin time in males in the 300 mg/kg group were also considered to be changes accompanying increased hepatic function.

Effects on the spleen were the significantly high absolute and relative spleen weights in

males in the groups of 30 mg/kg and higher doses. However, spleen weights were all within the range of historical control data, and the significant differences were likely to be due to relatively low spleen weights in the control group. The slight increase in the extramedullary hematopoiesis in 4 males and 1 female and significantly high reticulocyte counts in males in the 300 mg/kg group indicated slightest effects on the hematopoietic system, though no changes were noted in the erythrocyte parameters.

Absolute and relative thyroids weights tended to be high or were significantly high in males and females in the 300 mg/kg group. Regarding these changes, relation to the test substance administration was indicated by the significantly low total cholesterol and triglyceride in males in the 300 mg/kg group, and a possibility of onset of thyroid adenoma, etc. caused by lithium administration[3]. Triglyceride was significantly low in females in the 30 and 100 mg/kg groups, which was not dose dependent.

No changes related to the test substance administration were noted in urinalysis or autopsy findings.

In the recovery study after withdrawal, relative liver weight was significantly high in males in the 300 mg/kg group during 14 days from the day after the end of dosing; however, the increase was slight in degree. The low total cholesterol and triglyceride at the end of dosing were conversely high, and other changes disappeared in the recovery period. Thus, recovering tendency was observed on the whole.

As described above, changes related to the test substance administration were as follows: absolute and relative liver weights were high or tended to be high in males in the groups of 100 mg/kg or higher doses, and effects were noted in general appearance, detailed clinical observation, food consumption, liver, spleen, thyroids, etc. in males and females in the 300 mg/kg group. However, a recovering tendency was noted during withdrawal for 14 days.

Based on these results, No-observed-effect level (NOEL) of
was considered to be 30 mg/kg/day in males and 100 mg/kg/day in females under the conditions of the present study.

REFERENCES

1) Mariko Shirota, et al. Combined repeat dose and reproductive/developmental toxicity screening test of Lithium bromide by oral administration in rats, toxicity testing reports of environmental chemicals (10), pp. 329-346. Chemicals Investigation Promoting Council. 2003.

2) "Lithium carbonate tablet" product labeling. Mitsubishi Tanabe Pharma Corporation, Yoshitomiyakuhin Corporation, and Zensei Pharmaceutical Industries Co., Ltd. 2009.

3) R. A. Goyer. "Casarett and Doull's Toxicology, The Basic Science of Poisons," 5th ed. By C. D. Klaassen. McGraw-Hill. New York. pp. 724-725. 1996.

ENVIRONMENTAL FACTORS THAT MIGHT HAVE AFFECTED THE RELIABILITY OF THE TEST RESULTS

No environmental factors that might have affected the reliability of the test results were found.

STORAGE OF DOCUMENTS AND MATERIALS

The following documents and materials will be stored in the archives of Safety Research Institute for Chemical Compounds Co., Ltd. for 10 years after the study completion. Their storage thereafter will be decided on agreement with the study sponsor.

1. Study protocol and study protocol amendments
2. Raw data and other documents
3. Final report
4. Specimens: a. Blood specimens
   b. Fixed organs and tissues
   c. Microscopic specimens (paraffin-embedded specimens and sections)
5. A sample of the test substance

NAME AND SEAL OF STUDY DIRECTOR

Name and seal affixed in the original	August 11, 2010
Masao Sunaga, D.V.M., Study Director	Date

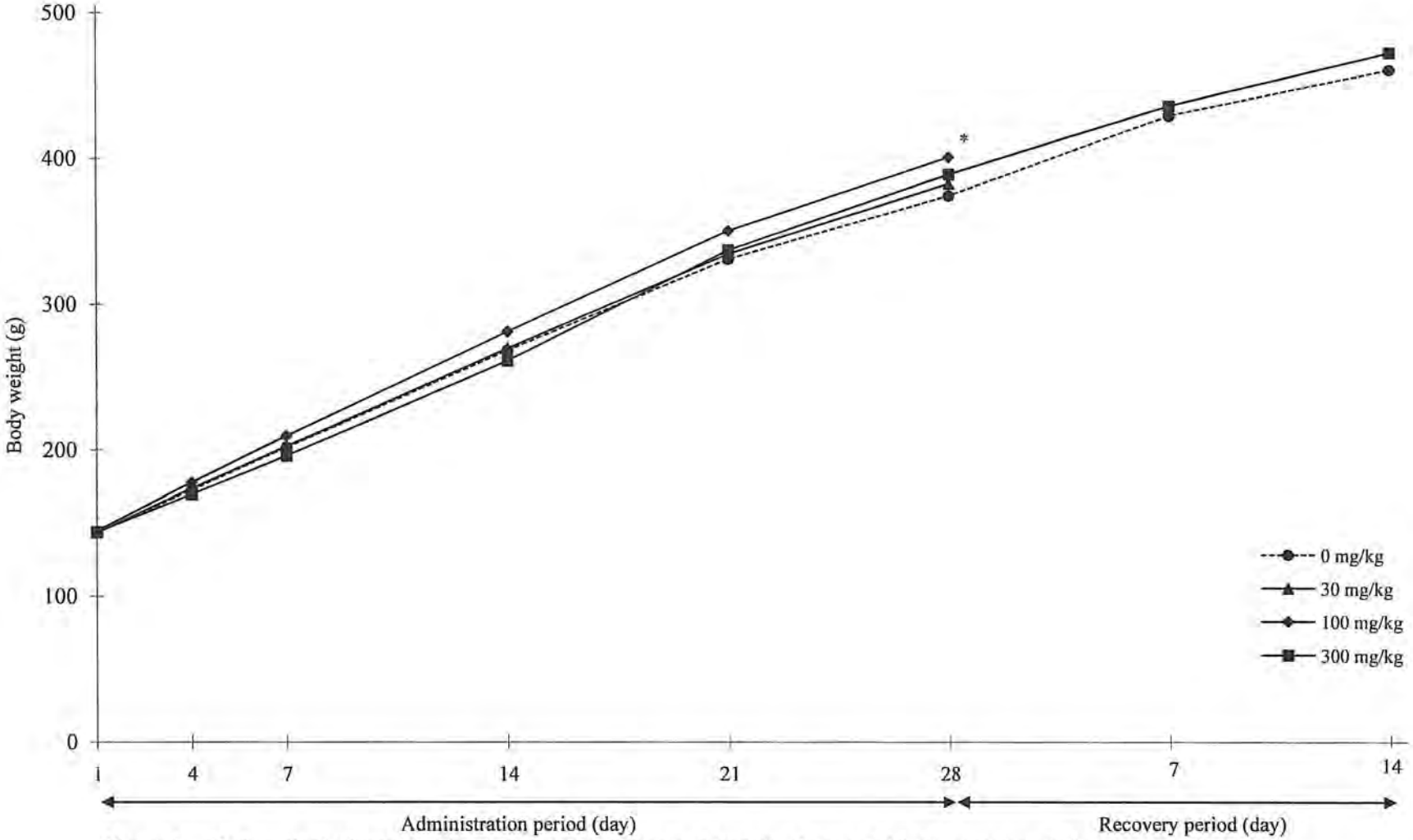

Figure 1 Body weight of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

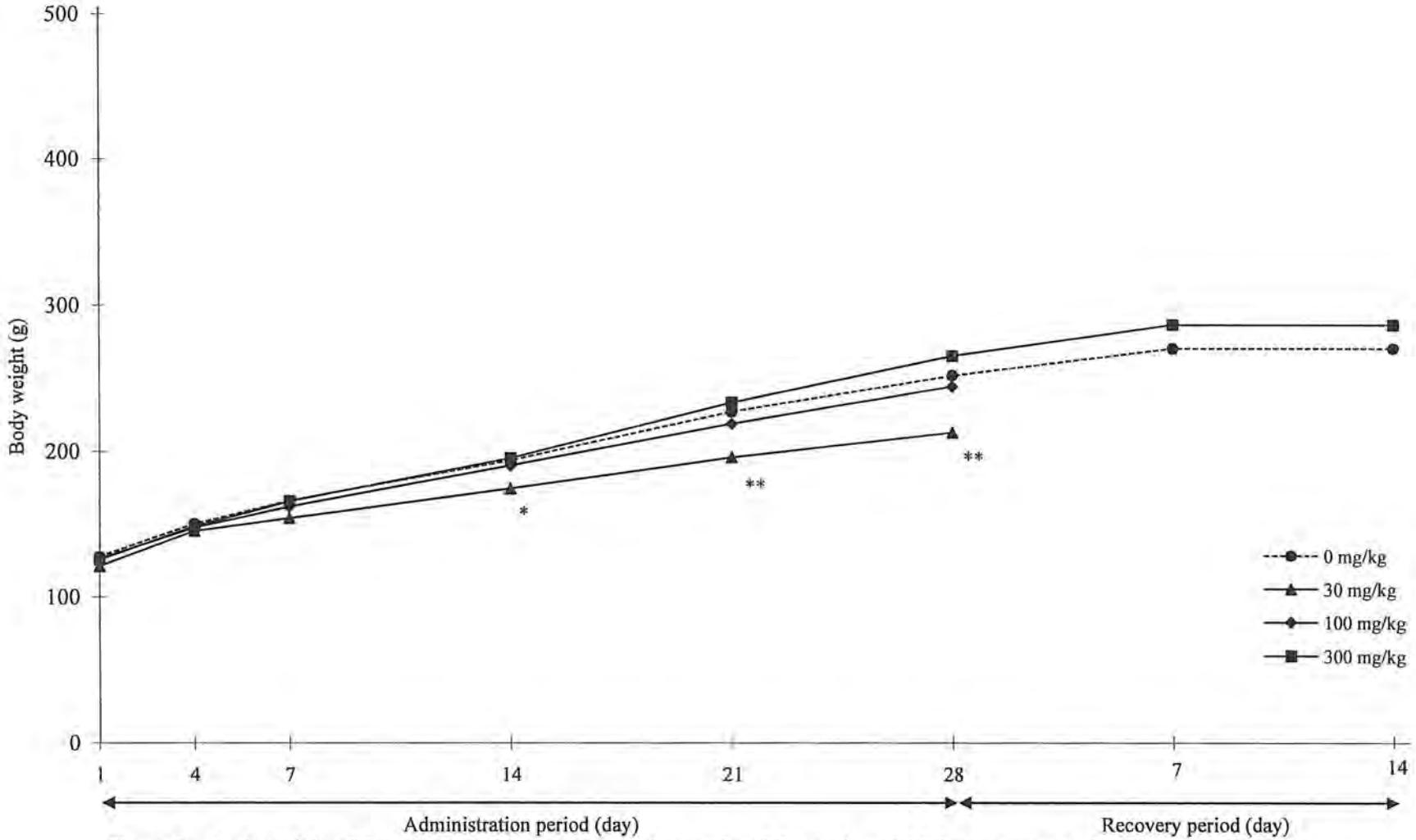

Figure 2 Body weight of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

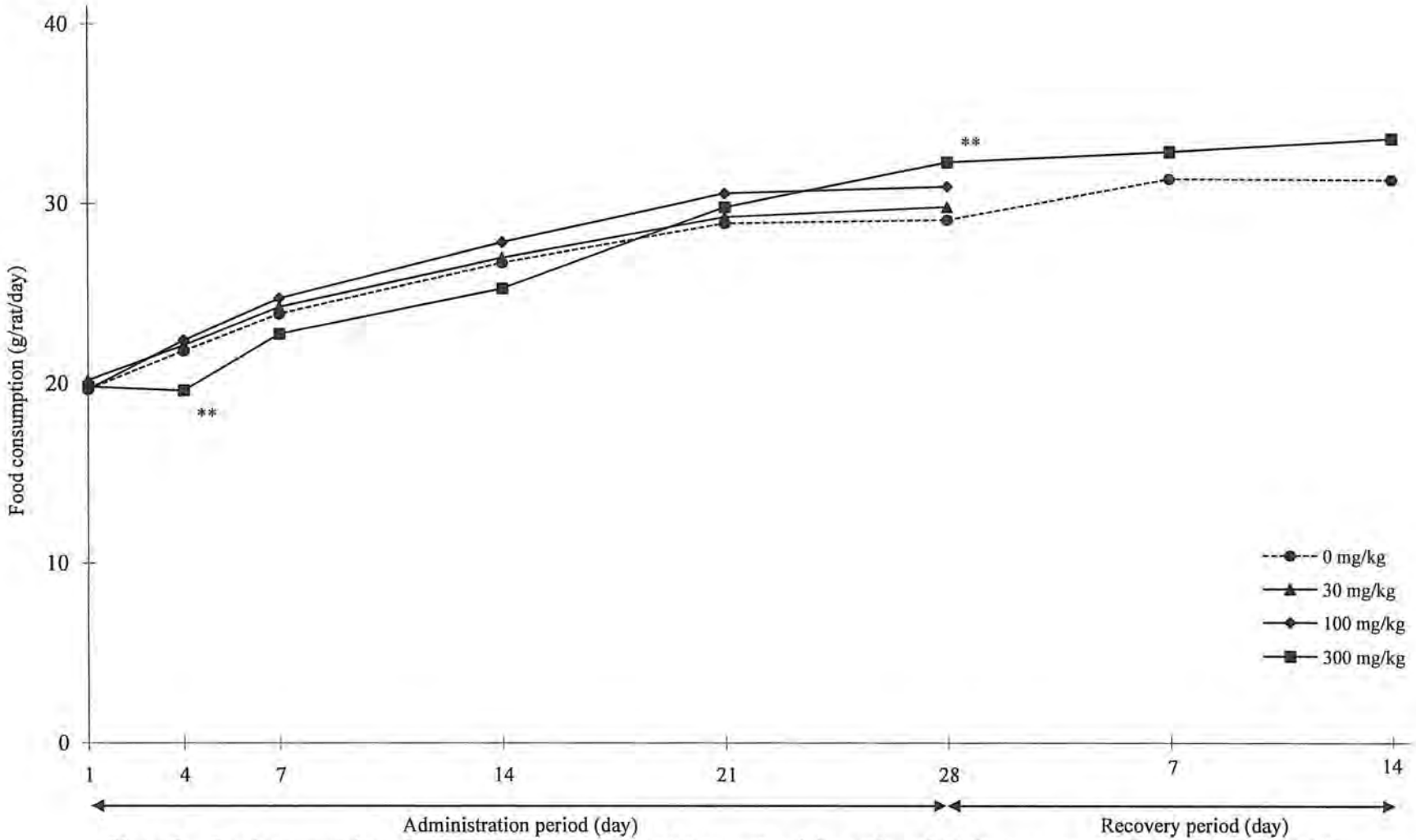

Figure 3 Food consumption of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

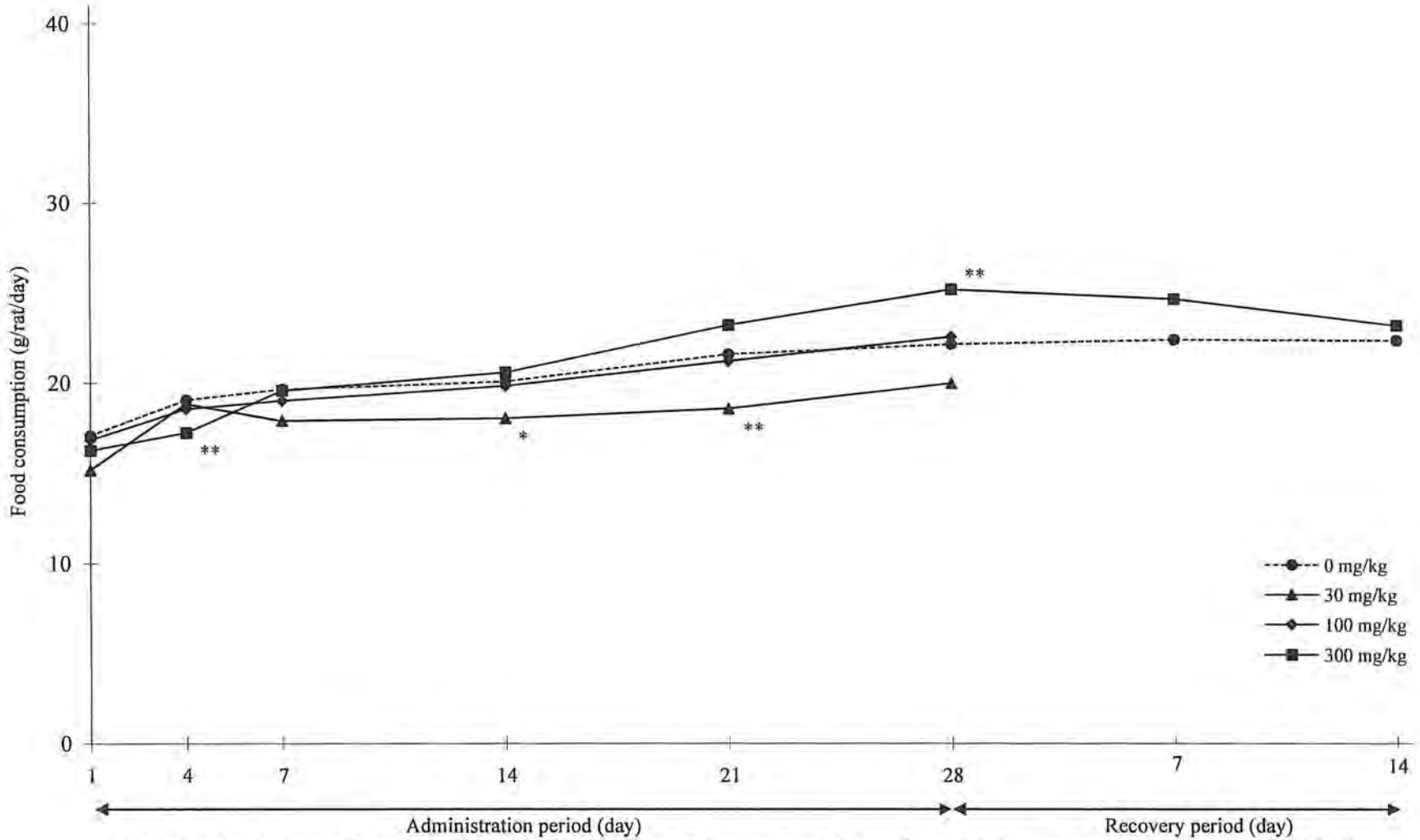

Figure 4 Food consumption of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

Table 1 General appearance of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Group	Findings	Administration period (day)														
		1	2	3	4	5	6	7	8	9	10	11,12	13,14	15	16	17
0 mg/kg	Number of animals examined	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No abnormal findings	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
30 mg/kg	Number of animals examined	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	No abnormal findings	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
100 mg/kg	Number of animals examined	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	No abnormal findings	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
300 mg/kg	Number of animals examined	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No abnormal findings	8	0	1	2	2	2	9	8	9	10	10	12	11	9	12
	Staggering gait	2	0	2	2	3	1	0	1	1	0	0	0	0	0	0
	Tachypnea	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
	Tremor	4	12	11	10	10	10	3	3	2	2	2	0	0	3	0

Group	Findings	Administration period (day)									Autopsy day	Recovery period (day) 1 - 14	Autopsy day
		18	19	20	21	22	23	24,25	26,27	28			
0 mg/kg	Number of animals examined	12	12	12	12	12	12	12	12	12	6	6	6
	No abnormal findings	12	12	12	12	12	12	12	12	12	6	6	6
30 mg/kg	Number of animals examined	6	6	6	6	6	6	6	6	6	6	-	-
	No abnormal findings	6	6	6	6	6	6	6	6	6	6	-	-
100 mg/kg	Number of animals examined	6	6	6	6	6	6	6	6	6	6	-	-
	No abnormal findings	6	6	6	6	6	6	6	5	5	5	-	-
	Scab at dorsal region	0	0	0	0	0	0	0	1	1	1	-	-
300 mg/kg	Number of animals examined	12	12	12	12	12	12	12	12	12	6	6	6
	No abnormal findings	10	8	11	9	8	8	9	10	7	6	6	6
	Jumping	2	1	1	3	4	3	3	2	5	0	0	0
	Tachypnea	0	0	0	1	0	0	0	0	0	0	0	0
	Tremor	0	3	0	0	0	1	0	0	0	0	0	0

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Table 2 General appearance of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Group	Findings	Administration period (day)																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
0 mg/kg	Number of animals examined	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No abnormal findings	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
30 mg/kg	Number of animals examined	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	No abnormal findings	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
100 mg/kg	Number of animals examined	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	No abnormal findings	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
300 mg/kg	Number of animals examined	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	No abnormal findings	7	0	0	2	0	1	5	8	10	6	6	10	10	9	9	8	11
	Staggering gait	2	5	0	4	1	2	1	2	1	1	0	0	1	0	1	1	0
	Tremor	5	11	12	9	12	11	6	3	2	6	6	2	1	3	3	4	1

Group	Findings	Administration period (day)											Autopsy	Recovery period (day)	Autopsy
		18	19	20	21	22	23	24	25	26	27	28	day	1 - 14	day
0 mg/kg	Number of animals examined	12	12	12	12	12	12	12	12	12	12	12	6	6	6
	No abnormal findings	12	12	12	12	12	12	12	12	12	12	12	6	6	6
30 mg/kg	Number of animals examined	6	6	6	6	6	6	6	6	6	6	6	6	-	-
	No abnormal findings	6	6	6	6	6	6	6	6	6	6	6	6	-	-
100 mg/kg	Number of animals examined	6	6	6	6	6	6	6	6	6	6	6	6	-	-
	No abnormal findings	6	6	6	6	6	6	5	5	5	6	6	6	-	-
	Tremor	0	0	0	0	0	0	1	1	1	0	0	0	-	-
300 mg/kg	Number of animals examined	12	12	12	12	12	12	12	12	12	12	12	6	6	6
	No abnormal findings	12	10	11	11	8	10	9	7	11	9	10	5	6	6
	Crushing of left tooth	0	0	0	0	0	0	0	0	0	1	1	1	0	0
	Jumping	0	0	0	1	2	1	1	0	0	1	0	0	0	0
	Staggering gait	0	0	0	1	1	0	0	1	0	0	0	0	0	0
	Tachypnea	0	0	0	1	0	0	0	1	0	0	0	0	0	0
	Tremor	0	2	1	0	3	1	2	4	1	3	2	0	0	0

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Table 3 Detailed clinical observation, in the cage, of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	Group	Number of animals	Category	Body position/ Posture	Respiratory pattern	Tremor/ Convulsion		Stereotype		Bizarre behavior
								Rolling	Repetitive circling	Biting/ Selfmutilation
				1	1	1	3	0	0	1
Pre	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	12	0	12	12	12
Day 7	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	9	3	12	12	12
Day 14	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	12	0	12	12	12
Day 21	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	12	0	12	12	12
Day 28	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	12	0	12	12	12
R-Day 7	0 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	6		6	6	6	0	6	6	6
R-Day 14	0 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	6		6	6	6	0	6	6	6

Values are expressed as the number of animals.
Category : The category number observed in each item.

Pre : Pre-administration.
Day 7 : Day 7 of administration.
Day 14 : Day 14 of administration.
Day 21 : Day 21 of administration.
Day 28 : Day 28 of administration.
R-Day 7 : Day 7 of recovery.
R-Day 14 : Day 14 of recovery.

Table 4 Detailed clinical observation, on the hand, of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	Group	Number of animals	Category	Ease of Removal 1	Ease of Handling 1	Muscle tone 2	Piloerection 1	Fur 1	Eyes 1	Mucous membranes 0	Skin 1	Pupil size 1	Lacrimation 1	Salivation 1	Secretions/ Excretions 0
Pre	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
Day 7	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
Day 14	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
Day 21	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
Day 28	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
R-Day 7	0 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
R-Day 14	0 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6

Values are expressed as the number of animals.
Category : The category number observed in each item.

Pre : Pre-administration.
Day 7 : Day 7 of administration.
Day 14 : Day 14 of administration.
Day 21 : Day 21 of administration.
Day 28 : Day 28 of administration.
R-Day 7 : Day 7 of recovery.
R-Day 14 : Day 14 of recovery.

Table 5 Detailed clinical observation, in the open-field, of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	Group	Number of animals	Category	Gait	Co-ordination of movement	Reactivity to environmental stimuli	Searching	Urination		Defecation		Stereotype		Bizarre behavior		Aggression
												Excessive grooming	Unusual head movement	Walking backward	Vocaliza-tion	
				1	1	1	1	0	1	0	1	0	0	1	1	1
Pre	0 mg/kg	12		12	12	12	12	5	7	10	2	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	2	4	5	1	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	3	3	6	0	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	7	5	11	1	12	12	12	12	12
Day 7	0 mg/kg	12		12	12	12	12	8	4	11	1	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	0	5	1	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	5	1	5	1	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	9	3	11	1	12	12	12	12	12
Day 14	0 mg/kg	12		12	12	12	12	8	4	11	1	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	0	5	1	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	5	1	6	0	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	9	3	11	1	12	12	12	12	12
Day 21	0 mg/kg	12		12	12	12	12	10	2	12	0	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	0	5	1	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	0	6	0	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	10	2	12	0	12	12	12	12	12
Day 28	0 mg/kg	12		12	12	12	12	11	1	11	1	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	0	5	1	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	5	1	5	1	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	9	3	12	0	12	12	12	12	12
R-Day 7	0 mg/kg	6		6	6	6	6	4	2	6	0	6	6	6	6	6
	300 mg/kg	6		6	6	6	6	5	1	6	0	6	6	6	6	6
R-Day 14	0 mg/kg	6		6	6	6	6	6	0	6	0	6	6	6	6	6
	300 mg/kg	6		6	6	6	6	5	1	6	0	6	6	6	6	6

Values are expressed as the number of animals.
Category : The category number observed in each item.

Pre : Pre-administration.
Day 7 : Day 7 of administration.
Day 14 : Day 14 of administration.
Day 21 : Day 21 of administration.
Day 28 : Day 28 of administration.
R-Day 7 : Day 7 of recovery.
R-Day 14 : Day 14 of recovery.

Table 6 Detailed clinical observation, in the cage, of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study (SR09244)

Period	Group	Number of animals	Category	Body position/ Posture	Respiratory pattern	Tremor/ Convulsion		Stereotype		Bizarre behavior
								Rolling	Repetitive circling	Biting/ Selfmutilation
				1	1	1	3	0	0	1
Pre	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	12	0	12	12	12
Day 7	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	8	4	12	12	12
Day 14	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	10	2	12	12	12
Day 21	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	12	0	12	12	12
Day 28	0 mg/kg	12		12	12	12	0	12	12	12
	30 mg/kg	6		6	6	6	0	6	6	6
	100 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	12		12	12	10	2	12	12	12
R-Day 7	0 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	6		6	6	6	0	6	6	6
R-Day 14	0 mg/kg	6		6	6	6	0	6	6	6
	300 mg/kg	6		6	6	6	0	6	6	6

Values are expressed as the number of animals.
Category : The category number observed in each item.

Pre : Pre-administration. Day 14 : Day 14 of administration. Day 28 : Day 28 of administration. R-Day 14 : Day 14 of recovery.
Day 7 : Day 7 of administration. Day 21 : Day 21 of administration. R-Day 7 : Day 7 of recovery.

Table 7 Detailed clinical observation, on the hand, of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	Group	Number of animals	Category	Ease of Removal 1	Ease of Handling 1	Muscle tone 2	Piloerection 1	Fur 1	Eyes 1	Mucous membranes 0	Skin 1	Pupil size 1	Lacrimation 1	Salivation 1	Secretions/ Excretions 0
Pre	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
Day 7	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
Day 14	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
Day 21	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
Day 28	0 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
	30 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	100 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	12		12	12	12	12	12	12	12	12	12	12	12	12
R-Day 7	0 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
R-Day 14	0 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6
	300 mg/kg	6		6	6	6	6	6	6	6	6	6	6	6	6

Values are expressed as the number of animals.

Category : The category number observed in each item.

Pre : Pre-administration.
Day 7 : Day 7 of administration.
Day 14 : Day 14 of administration.
Day 21 : Day 21 of administration.
Day 28 : Day 28 of administration.
R-Day 7 : Day 7 of recovery.
R-Day 14 : Day 14 of recovery.

Table 8 Detailed clinical observation, in the open-field, of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	Group	Number of animals	Category	Gait	Co-ordination of movement		Reactivity to environmental stimuli	Searching	Urination		Defecation		Stereotype		Bizarre behavior		Aggression
													Excessive grooming	Unusual head movement	Walking backward	Vocalization	
				1	0	1	1	1	0	1	0	1	0	0	1	1	1
Pre	0 mg/kg	12		12	0	12	12	12	9	3	10	2	12	12	12	12	12
	30 mg/kg	6		6	0	6	6	6	4	2	5	1	6	6	6	6	6
	100 mg/kg	6		6	0	6	6	6	4	2	6	0	6	6	6	6	6
	300 mg/kg	12		12	0	12	12	12	10	2	11	1	12	12	12	12	12
Day 7	0 mg/kg	12		12	0	12	12	12	11	1	12	0	12	12	12	12	12
	30 mg/kg	6		6	0	6	6	6	6	0	5	1	6	6	6	6	6
	100 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6
	300 mg/kg	12		12	1	11	12	12	11	1	11	1	12	12	12	12	12
Day 14	0 mg/kg	12		12	0	12	12	12	12	0	12	0	12	12	12	12	12
	30 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6
	100 mg/kg	6		6	0	6	6	6	5	1	6	0	6	6	6	6	6
	300 mg/kg	12		12	0	12	12	12	12	0	12	0	12	12	12	12	12
Day 21	0 mg/kg	12		12	0	12	12	12	12	0	12	0	12	12	12	12	12
	30 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6
	100 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6
	300 mg/kg	12		12	1	11	12	12	12	0	12	0	12	12	12	12	12
Day 28	0 mg/kg	12		12	0	12	12	12	12	0	12	0	12	12	12	12	12
	30 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6
	100 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6
	300 mg/kg	12		12	0	12	12	12	12	0	12	0	12	12	12	12	12
R-Day 7	0 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6
	300 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6
R-Day 14	0 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6
	300 mg/kg	6		6	0	6	6	6	6	0	6	0	6	6	6	6	6

Values are expressed as the number of animals.

Category : The category number observed in each item.

Pre : Pre-administration.
Day 7 : Day 7 of administration.
Day 14 : Day 14 of administration.
Day 21 : Day 21 of administration.
Day 28 : Day 28 of administration.
R-Day 7 : Day 7 of recovery.
R-Day 14 : Day 14 of recovery.

Table 9 Functional observation of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	Group	Number of animals	Category	Reactivity						Righting reflex	
				Visual	Touch	Auditory		Pain	Proprioceptive		
				4	2	1	2	2	1	1	2
Week 4	0 mg/kg	12		12	12	12	0	12	12	12	0
	30 mg/kg	6		6	6	6	0	6	6	6	0
	100 mg/kg	6		6	6	6	0	6	6	6	0
	300 mg/kg	12		12	12	9	3	12	12	[6	6]+
R-Week 2	0 mg/kg	6		6	6	6	0	6	6	6	0
	300 mg/kg	6		6	6	6	0	6	6	6	0

Values are expressed as the number of animals.
Category : The category number observed in each item.

Week 4 : Week 4 of administration.
R-Week 2 : Week 2 of recovery.

Visual reactivity: approach response.
Touch reactivity: touch response.
Auditory reactivity: response to Galton's whistle.
Pain reactivity: tail pinch response.
Proprioceptive reactivity: returning from enforced posture.
Righting reflex: landing performance from 30 cm above.

[ ]+ : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Mann-Whitney's U-test).

Table 10 Functional observation of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	Group	Number of animals	Category	Reactivity					Righting reflex	
				Visual	Touch	Auditory	Pain	Proprioceptive		
				4	2	1	2	1	1	2
Week 4	0 mg/kg	12		12	12	12	12	12	12	0
	30 mg/kg	6		6	6	6	6	6	6	0
	100 mg/kg	6		6	6	6	6	6	6	0
	300 mg/kg	12		12	12	12	12	12	10	2
R-Week 2	0 mg/kg	6		6	6	6	6	6	6	0
	300 mg/kg	6		6	6	6	6	6	6	0

Values are expressed as the number of animals.
Category : The category number observed in each item.

Week 4 : Week 4 of administration.
R-Week 2 : Week 2 of recovery.

Visual reactivity: approach response.
Touch reactivity: touch response.
Auditory reactivity: response to Galton's whistle.
Pain reactivity: tail pinch response.
Proprioceptive reactivity: returning from enforced posture.
Righting reflex: landing performance from 30 cm above.

Table 11 Grip strength and motor activity measurements of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	Group	Number of animals		Grip strength Forelimb (g)	Grip strength Hindlimb (g)	Motor activity measurements (count) 0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total
Week 4	0 mg/kg	12	Mean	1108.23	376.13	432.7	306.8	245.7	213.9	177.1	151.1	1527.2
			S.D.	133.59	67.68	174.8	151.6	121.0	132.2	92.9	92.9	688.2
	30 mg/kg	6	Mean	1085.67	383.00	382.8	283.7	189.3	182.5	124.2	168.5	1331.0
			S.D.	67.01	70.24	106.4	167.1	161.2	252.9	174.8	158.6	961.8
	100 mg/kg	6	Mean	1057.38	391.95	458.7	246.8	155.0	191.7	122.5	167.5	1342.2
			S.D.	107.32	81.79	128.8	189.5	91.4	87.6	130.0	38.1	459.8
	300 mg/kg	12	Mean	931.16**	385.83	280.9	192.3	124.2*	128.8	93.3	43.7++	863.1
			S.D.	90.04	79.74	184.3	141.8	81.6	110.0	96.6	58.3	568.1
R-week 2	0 mg/kg	6	Mean	1409.33	500.72	490.3	446.2	356.3	279.5	240.7	228.3	2041.3
			S.D.	138.32	125.06	154.7	152.7	102.8	151.6	156.2	215.8	824.9
	300 mg/kg	6	Mean	1404.28	458.28	443.7	288.2	242.3	174.7	160.5	117.5	1426.8
			S.D.	98.41	40.38	107.0	92.1	115.4	102.8	117.3	68.1	432.0

Week 4 : Week 4 of administration.

R-week 2 : Week 2 of recovery.

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

++ : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Mann-Whitney's U-test).

Table 12 Grip strength and motor activity measurements of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	Group	Number of animals		Grip strength		Motor activity measurements (count)						
				Forelimb (g)	Hindlimb (g)	0'-10'	10'-20'	20'-30'	30'-40'	40'-50'	50'-60'	Total
Week 4	0 mg/kg	12	Mean	918.75	320.99	664.3	423.9	360.1	287.3	258.8	244.3	2238.7
			S.D.	133.88	49.01	239.3	225.9	185.8	184.2	161.5	119.3	954.7
	30 mg/kg	6	Mean	859.65	308.67	649.5	463.7	428.0	364.5	315.8	159.2	2380.7
			S.D.	146.88	29.13	173.5	97.8	125.8	96.2	163.0	62.3	605.9
	100 mg/kg	6	Mean	910.05	329.12	929.0	568.3	399.3	340.8	343.0	181.8	2762.3
			S.D.	120.20	54.72	342.5	159.1	225.0	191.6	200.8	175.6	1238.1
	300 mg/kg	12	Mean	885.51	380.63*	605.5	424.4	325.6	283.2	234.3	198.7	2071.7
			S.D.	118.20	61.98	309.1	248.1	215.0	204.0	192.6	221.9	1148.4
R-week 2	0 mg/kg	6	Mean	1043.63	422.65	661.0	480.2	369.7	298.8	205.0	141.8	2156.5
			S.D.	61.71	90.85	239.4	139.7	114.8	90.5	158.2	126.8	564.5
	300 mg/kg	6	Mean	1151.60	440.17	597.5	364.0	263.5	291.8	205.8	85.0	1807.7
			S.D.	139.27	86.27	267.1	245.9	215.6	219.6	323.3	109.4	1327.2

Week 4 : Week 4 of administration.

R-week 2 : Week 2 of recovery.

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

Table 13 Body weight of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Group	Number of animals		Body weight (g) Administration period (day) 1	4	7	14	21	28	Body weight gain 1-28 g	%	Body weight (g) Recovery period (day) 7	14	Body weight gain 0-14 g	%
											(6)	(6)	(6)	(6)
0 mg/kg	12	Mean	143.4	172.7	201.8	268.4	330.8	374.3	230.8	160.869	429.3	460.8	80.7	21.145
		S.D.	3.8	6.0	6.8	11.7	15.2	20.0	17.5	10.175	31.6	37.2	13.4	2.560
30 mg/kg	6	Mean	143.8	173.7	202.5	269.8	334.2	382.5	238.7	165.863	-	-	-	-
		S.D.	4.0	5.4	6.4	9.3	14.1	20.0	17.2	9.767	-	-	-	-
100 mg/kg	6	Mean	144.8	177.8	209.7	281.2	350.2	400.8*	256.0*	176.805*	-	-	-	-
		S.D.	5.0	6.6	8.0	14.9	16.7	21.9	19.9	13.167	-	-	-	-
											(6)	(6)	(6)	(6)
300 mg/kg	12	Mean	144.0	169.7	196.0	261.3	336.9	389.0	245.0	170.189	436.0	472.5	77.2	19.535
		S.D.	3.4	5.4	7.7	11.8	16.4	18.7	18.0	12.592	17.6	21.9	8.3	2.061

Values in parentheses are number of animals.

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

- : Blank.

Table 14 Body weight of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Group	Number of animals		Body weight (g) Administration period (day) 1	4	7	14	21	28	Body weight gain 1-28 g	%	Body weight (g) Recovery period (day) 7	14	Body weight gain 0-14 g	%
0 mg/kg	12	Mean	127.9	150.4	166.3	193.8	227.0	251.8	123.8	96.406	(6) 270.5	(6) 279.3	(6) 33.2	(6) 13.570
		S.D.	7.8	8.9	12.9	14.7	23.2	26.8	19.9	10.971	27.2	24.9	8.5	3.622
30 mg/kg	6	Mean	121.3	145.3	154.3	174.5*	195.8**	212.8**	91.5*	75.540*	-	-	-	-
		S.D.	10.0	11.3	15.6	20.0	19.3	29.1	25.9	20.909	-	-	-	-
100 mg/kg	6	Mean	126.3	147.7	162.2	190.3	218.8	244.3	118.0	93.037	-	-	-	-
		S.D.	7.6	9.3	12.8	15.7	22.6	24.9	17.8	9.581	-	-	-	-
300 mg/kg	12	Mean	125.8	148.6	165.8	195.3	233.3	265.3	139.5	111.150	(6) 286.7	(6) 297.0	(6) 29.2	(6) 10.865
		S.D.	5.0	5.0	8.2	12.1	13.2	19.8	20.4	18.282	21.1	28.6	19.1	6.986

Values in parentheses are number of animals.

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

- : Blank.

Table 15 Food consumption of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Group	Number of animals		Food consumption (g/rat/day)							
			Administration period (day)						Recovery period (day)	
			1	4	7	14	21	28	7	14
0 mg/kg	12	Mean	19.67	21.80	23.84	26.68	28.88	29.08	(6) 31.37	(6) 31.32
		S.D.	1.67	1.19	1.02	1.49	1.70	1.87	1.37	2.32
30 mg/kg	6	Mean	20.17	22.10	24.22	26.95	29.23	29.80	-	-
		S.D.	1.60	1.77	1.80	1.83	2.38	2.93	-	-
100 mg/kg	6	Mean	19.67	22.38	24.70	27.82	30.55	30.93	-	-
		S.D.	1.37	1.47	1.54	2.20	2.30	2.29	-	-
300 mg/kg	12	Mean	19.83	19.61**	22.73	25.25	29.78	32.30**	(6) 32.87	(6) 33.60
		S.D.	1.64	1.24	1.27	1.86	2.59	2.37	1.56	1.73

Values in parentheses are number of animals.

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

- : Blank.

Table 16 Food consumption of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Group	Number of animals		Food consumption (g/rat/day)							
			Administration period (day)						Recovery period (day)	
			1	4	7	14	21	28	7	14
0 mg/kg	12	Mean	17.08	19.04	19.64	20.08	21.60	22.16	22.40 (6)	22.35 (6)
		S.D.	1.62	1.09	1.70	1.64	2.26	1.78	1.34	1.88
30 mg/kg	6	Mean	15.17	18.83	17.90	18.03*	18.57**	19.98	-	-
		S.D.	2.93	1.98	1.96	1.82	1.50	2.10	-	-
100 mg/kg	6	Mean	16.83	18.55	19.00	19.83	21.22	22.57	-	-
		S.D.	2.23	0.81	1.51	1.67	2.40	1.34	-	-
300 mg/kg	12	Mean	16.25	17.23**	19.57	20.58	23.22	25.20**	24.67 (6)	23.18 (6)
		S.D.	1.60	0.91	1.25	1.44	1.05	2.65	3.15	3.20

Values in parentheses are number of animals.

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

- : Blank.

Table 17 Urinary findings of male rats in 28-day repeated dose oral toxicity study of (SR09244)

Group	Number of animals	pH			Protein			Glucose	Ketone body	Urobili-nogen	Bili-rubin	Occult blood		
		7.5	8.0	8.5	-	±	1+	-	-	0.1 EU/dL	-	-	±	1+
0 mg/kg	12	0	1	11	0	7	5	12	12	12	12	11	1	0
30 mg/kg	6	0	2	4	0	3	3	6	6	6	6	4	2	0
100 mg/kg	6	0	2	4	0	4	2	6	6	6	6	4	1	1
300 mg/kg	12	1	5	6	0	9	3	12	12	12	12	11	1	0

Group	Number of animals	Color	Specific gravity				Urine volume (mL/21hr, mean±S.D.)
		A	1.011-1.020	1.021-1.030	1.031-1.040	1.041-1.050	
0 mg/kg	12	12	1	4	6	1	22.33 ± 9.34
30 mg/kg	6	6	1	3	2	0	30.25 ± 11.96
100 mg/kg	6	6	1	4	1	0	30.58 ± 8.80
300 mg/kg	12	12	2	9	1	0	28.88 ± 7.85

Values are number of animals with findings.
- ; Normal, ± ; Slight, 1+ ; Moderate.
Color : A; Pale yellow or yellow.

Table 18 Urinary findings of female rats in 28-day repeated dose oral toxicity study of (SR09244)

Group	Number of animals	pH					Protein			Glucose	Ketone body	Urobilinogen	Bilirubin	Occult blood				
		6.5	7.0	7.5	8.0	8.5	-	±	1+	-	-	0.1 EU/dL	-	-	±	1+	2+	3+
0 mg/kg	12	1	1	1	1	8	5	7	0	12	12	12	12	8	3	0	0	1
30 mg/kg	6	0	0	1	3	2	1	4	1	6	6	6	6	6	0	0	0	0
100 mg/kg	6	0	0	0	2	4	2	4	0	6	6	6	6	3	3	0	0	0
300 mg/kg	12	1	0	1	4	6	4	8	0	12	12	12	12	12	0	0	0	0

Group	Number of animals	Color A	Specific gravity					Urine volume (mL/21hr, mean±S.D.)
			1.011-1.020	1.021-1.030	1.031-1.040	1.041-1.050	1.050<	
0 mg/kg	12	12	1	3	4	4	0	17.17 ± 11.07
30 mg/kg	6	6	0	2	3	0	1	10.25 ± 4.32
100 mg/kg	6	6	1	1	2	2	0	20.50 ± 18.81
300 mg/kg	12	12	1	4	7	0	0	18.25 ± 5.24

Values are number of animals with findings.
- ; Normal, ± ; Slight, 1+ ; Moderate, 2+ ; Severe, 3+ ; Very severe.
Color : A; Pale yellow or yellow.

Table 19 Urinary findings of male rats in 14-day recovery study following 28-day repeated oral dose of (SR09244)

Group	Number of animals	pH			Protein			Glucose	Ketone body	Urobili-nogen	Bili-rubin	Occult blood
		7.5	8.0	8.5	-	±	1+	-	-	0.1 EU/dL	-	-
0 mg/kg	6	0	2	4	0	3	3	6	6	6	6	6
300 mg/kg	6	1	0	5	0	1	5	6	6	6	6	6

Group	Number of animals	Color	Specific gravity			Urine volume (mL/21hr, mean±S.D.)
		A	1.011-1.020	1.021-1.030	1.031-1.040	
0 mg/kg	6	6	3	2	1	38.83 ± 17.53
300 mg/kg	6	6	1	2	3	29.08 ± 7.92

Values are number of animals with findings.
- ; Normal, ± ; Slight, 1+ ; Moderate.
Color : A; Pale yellow or yellow.

Table 20 Urinary findings of female rats in 14-day recovery study following 28-day repeated oral dose of (SR09244)

Group	Number of animals	pH				Protein			Glucose	Ketone body	Urobili-nogen	Bili-rubin	Occult blood	
		7.0	7.5	8.0	8.5	-	±	1+	-	-	0.1 EU/dL	-	-	±
0 mg/kg	6	1	0	1	4	0	6	0	6	6	6	6	6	0
300 mg/kg	6	0	0	1	5	2	2	2	6	6	6	6	5	1

Group	Number of animals	Color	Specific gravity				Urine volume (mL/21hr, mean±S.D.)
		A	1.011-1.020	1.021-1.030	1.031-1.040	1.041-1.050	
0 mg/kg	6	6	1	1	2	2	19.17 ± 6.82
300 mg/kg	6	6	0	4	0	2	24.08 ± 9.36

Values are number of animals with findings.
- ; Normal, ± ; Slight, 1+ ; Moderate.
Color : A; Pale yellow or yellow.

Table 21 Hematological findings of male rats in 28-day repeated dose oral toxicity study of (SR09244)

Group	Number of animals		RBC $10^4/\mu L$	HCT %	HGB g/dL	MCV fL	MCH pg	MCHC g/dL	WBC $10^2/\mu L$	Platelet $10^4/\mu L$
0 mg/kg	6	Mean	804.2	45.22	15.68	56.23	19.48	34.68	95.87	121.10
		S.D.	18.4	1.67	0.53	1.87	0.58	0.26	25.56	16.82
30 mg/kg	6	Mean	804.5	44.33	15.55	55.22	19.35	35.07	111.45	120.13
		S.D.	40.5	0.79	0.36	2.49	0.79	0.28	16.34	16.44
100 mg/kg	6	Mean	798.8	44.22	15.52	55.40	19.43	35.08	134.20*	127.58
		S.D.	32.5	0.95	0.38	1.71	0.56	0.25	27.26	5.00
300 mg/kg	6	Mean	766.0	44.65	15.55	58.37	20.35	34.85	125.05	114.62
		S.D.	32.8	0.82	0.34	2.01	0.60	0.34	21.84	11.71

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

(to be continued)

Table 21 Hematological findings of male rats in 28-day repeated dose oral toxicity study of (SR09244) (continued)

Group	Number of animals		Reticulocyte %	PT sec	APTT sec	Differential count of WBC ($10^2/\mu L$)				
						Neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte
0 mg/kg	6	Mean	4.323	17.10	26.50	14.67	1.43	0.05	3.85	75.87
		S.D.	0.534	0.36	2.73	4.93	0.37	0.05	1.99	21.49
30 mg/kg	6	Mean	4.282	17.65	25.47	22.72	1.80	0.07	3.97	82.90
		S.D.	0.517	2.45	2.50	6.60	0.82	0.05	0.86	16.29
100 mg/kg	6	Mean	5.070	17.72	24.92	30.23+	1.90	0.05	3.98	98.03
		S.D.	0.253	0.61	1.62	17.02	0.46	0.05	1.60	14.22
300 mg/kg	6	Mean	5.337*	16.38+	22.75*	28.40++	1.82	0.02	4.30	90.52
		S.D.	0.910	0.40	0.91	6.66	0.51	0.04	1.96	14.63

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).
+ : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Mann-Whitney's U-test).
++ : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Mann-Whitney's U-test).

Table 22 Hematological findings of female rats in 28-day repeated dose oral toxicity study of (SR09244)

Group	Number of animals		RBC $10^4/\mu L$	HCT %	HGB g/dL	MCV fL	MCH pg	MCHC g/dL	WBC $10^2/\mu L$	Platelet $10^4/\mu L$
0 mg/kg	6	Mean	787.0	43.85	15.47	55.75	19.67	35.28	82.02	129.77
		S.D.	31.5	1.71	0.72	0.89	0.29	0.38	12.37	27.02
30 mg/kg	6	Mean	809.0	43.67	15.62	54.02	19.32	35.77	73.27	110.27
		S.D.	27.3	1.41	0.49	1.79	0.59	0.52	22.11	12.72
100 mg/kg	6	Mean	777.7	43.20	15.30	55.58	19.67	35.43	82.78	104.47
		S.D.	28.8	1.32	0.46	1.53	0.43	0.25	34.27	10.85
300 mg/kg	6	Mean	759.3	42.70	15.13	56.23	19.93	35.43	95.18	117.23
		S.D.	44.4	2.73	1.00	1.67	0.60	0.25	19.12	15.96

(to be continued)

Table 22 Hematological findings of female rats in 28-day repeated dose oral toxicity study of (SR09244) (continued)

Group	Number of animals		Reticulocyte %	PT sec	APTT sec	Differential count of WBC ($10^2/\mu L$)				
						Neutrophil	Eosinophil	Basophil	Monocyte	Lymphocyte
0 mg/kg	6	Mean	4.073	17.45	23.23	12.40	2.08	0.00	2.32	65.22
		S.D.	0.625	0.91	1.11	4.92	1.27	0.00	0.96	8.18
30 mg/kg	6	Mean	3.207	17.17	21.40*	10.85	1.43	0.00	2.38	58.60
		S.D.	0.931	0.73	0.62	4.05	0.97	0.00	1.32	22.07
100 mg/kg	6	Mean	4.062	16.93	22.60	11.48	1.92	0.02	2.33	67.03
		S.D.	0.634	0.87	1.31	6.09	1.26	0.04	1.36	30.00
300 mg/kg	6	Mean	4.565	17.23	21.43*	14.35	1.68	0.02	3.33	75.80
		S.D.	0.803	1.04	1.20	2.89	0.98	0.04	1.24	18.10

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

Table 23 Hematological findings of male rats in 14-day recovery study following 28-day repeated oral dose of (SR09244)

Group	Number of animals		RBC $10^4/\mu L$	HCT %	HGB g/dL	MCV fL	MCH pg	MCHC g/dL	WBC $10^2/\mu L$	Platelet $10^4/\mu L$
0 mg/kg	6	Mean	882.3	46.25	16.48	52.45	18.68	35.63	124.55	128.75
		S.D.	29.9	1.23	0.45	1.52	0.60	0.59	11.32	14.42
300 mg/kg	6	Mean	855.0	45.85	16.05	53.68	18.80	35.00*	113.37	123.28
		S.D.	33.6	0.75	0.24	2.28	0.66	0.36	10.23	10.78

Group	Number of animals		Reticulo-cyte %	PT sec	APTT sec	Differential count of WBC ($10^2/\mu L$)				
						Neutrophil	Eosinophil	Basophil	Monocyte	Lympho-cyte
0 mg/kg	6	Mean	3.637	17.27	25.93	24.07	1.55	0.07	4.42	94.45
		S.D.	0.396	1.77	2.33	2.68	0.51	0.05	1.20	10.32
300 mg/kg	6	Mean	3.740	17.12	25.80	17.63	2.10	0.07	5.25	88.32
		S.D.	0.714	1.06	2.11	6.90	0.73	0.05	1.15	7.32

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

Table 24 Hematological findings of female rats in 14-day recovery study following 28-day repeated oral dose of (SR09244)

Group	Number of animals		RBC $10^4/\mu L$	HCT %	HGB g/dL	MCV fL	MCH pg	MCHC g/dL	WBC $10^2/\mu L$	Platelet $10^4/\mu L$
0 mg/kg	6	Mean	816.5	43.32	15.52	53.08	19.02	35.80	70.05	115.67
		S.D.	35.2	1.23	0.55	1.18	0.42	0.29	16.31	13.68
300 mg/kg	6	Mean	807.2	42.98	15.38	53.30	19.07	35.78	61.00	101.43
		S.D.	28.8	0.82	0.37	2.04	0.75	0.23	10.71	10.10

Group	Number of animals		Reticulo-cyte %	PT sec	APTT sec	Differential count of WBC ($10^2/\mu L$)				
						Neutrophil	Eosinophil	Basophil	Monocyte	Lympho-cyte
0 mg/kg	6	Mean	3.347	16.53	20.48	12.10	1.50	0.02	1.77	54.67
		S.D.	0.505	0.62	1.06	4.72	0.57	0.04	0.81	14.06
300 mg/kg	6	Mean	2.808	16.37	20.77	8.72	1.42	0.00	2.07	48.80
		S.D.	0.923	0.72	1.39	1.82	0.25	0.00	0.52	9.90

Table 25 Biochemical findings of male rats in 28-day repeated dose oral toxicity study of (SR09244)

Group	Number of animals		TP g/dL	Albumin g/dL	A/G ratio	Protein fraction %					AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L	T-Bil mg/dL
						Albumin	Globulin								
							α_1	α_2	β	γ					
0 mg/kg	6	Mean	5.28	2.865	1.185	54.18	20.65	7.43	14.08	3.65	74.2	25.5	625.3	0.37	0.050
		S.D.	0.18	0.124	0.052	1.15	0.98	0.22	0.65	0.49	14.6	3.4	94.4	0.20	0.017
30 mg/kg	6	Mean	5.35	2.910	1.197	54.43	19.92	7.12	14.57	3.97	90.5	29.3	676.2	0.40	0.047
		S.D.	0.18	0.046	0.078	1.51	0.69	0.20	0.82	0.56	27.7	2.0	83.1	0.13	0.010
100 mg/kg	6	Mean	5.45	2.980	1.215	54.80	19.37	7.37	14.07	4.40	81.2	28.8	731.2	0.52	0.040
		S.D.	0.20	0.092	0.074	1.59	1.02	0.16	0.85	1.61	9.7	2.9	54.4	0.12	0.006
300 mg/kg	6	Mean	5.08	2.888	1.317**	56.83**	20.05	7.17	12.25**	3.70	94.8	38.0++	909.2**	0.50	0.035
		S.D.	0.13	0.074	0.041	0.79	1.11	0.45	0.87	0.54	9.8	10.6	84.0	0.09	0.010

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

++ : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Mann-Whitney's U-test).

(to be continued)

Table 25 Biochemical findings of male rats in 28-day repeated dose oral toxicity study of (SR09244) (continued)

Group	Number of animals		Glucose mg/dL	T-Cho mg/dL	TG mg/dL	UN mg/dL	Crea mg/dL	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
0 mg/kg	6	Mean	154.7	53.2	49.5	14.42	0.530	143.3	4.777	107.0	9.87	8.57
		S.D.	28.7	8.2	18.6	1.67	0.023	1.0	0.226	1.9	0.14	0.49
30 mg/kg	6	Mean	152.7	50.8	50.8	13.73	0.523	142.2	4.465	105.3	9.68	8.33
		S.D.	12.0	9.2	22.5	2.38	0.037	0.8	0.264	1.5	0.23	0.72
100 mg/kg	6	Mean	153.5	47.0	50.3	12.63	0.558	141.3**	4.535	104.5*	9.68	8.40
		S.D.	7.1	10.9	30.7	1.48	0.044	0.8	0.162	1.6	0.21	0.53
300 mg/kg	6	Mean	126.8	39.7*	20.7+	16.02	0.520	139.8**	4.513	103.3**	9.80	9.60*
		S.D.	11.3	6.1	6.1	3.91	0.027	1.2	0.322	0.8	0.22	0.86

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).
** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).
+ : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Mann-Whitney's U-test).

Table 26 Biochemical findings of female rats in 28-day repeated dose oral toxicity study of (SR09244)

Group	Number of animals		TP g/dL	Albumin g/dL	A/G ratio	Protein fraction %					AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L	T-Bil mg/dL
						Albumin	Globulin								
							α_1	α_2	β	γ					
0 mg/kg	6	Mean	5.70	3.118	1.212	54.72	18.43	7.88	13.78	5.18	67.0	20.7	390.0	0.52	0.047
		S.D.	0.20	0.121	0.090	1.85	0.64	0.36	0.98	0.94	8.9	2.7	58.5	0.19	0.015
30 mg/kg	6	Mean	5.72	3.163	1.243	55.35	17.90	7.65	13.58	5.52	67.2	22.3	426.0	0.48	0.057
		S.D.	0.24	0.145	0.058	1.10	1.11	0.37	0.66	1.22	4.1	1.8	62.9	0.15	0.010
100 mg/kg	6	Mean	5.75	3.173	1.235	55.20	17.78	7.58	13.63	5.80	67.0	21.7	436.8	0.52	0.045
		S.D.	0.16	0.054	0.063	1.31	1.40	0.34	0.51	1.73	5.2	3.2	138.1	0.16	0.016
300 mg/kg	6	Mean	5.62	3.143	1.270	55.93	17.93	7.57	13.05	5.52	71.3	24.5	434.0	0.55	0.053
		S.D.	0.18	0.161	0.073	1.42	0.31	0.27	1.03	1.17	19.6	4.6	98.9	0.14	0.022

(to be continued)

Table 26 Biochemical findings of female rats in 28-day repeated dose oral toxicity study of (SR09244) (continued)

Group	Number of animals		Glucose mg/dL	T-Cho mg/dL	TG mg/dL	UN mg/dL	Crea mg/dL	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
0 mg/kg	6	Mean	126.7	59.0	13.7	14.67	0.555	142.0	4.427	105.7	9.97	8.20
		S.D.	17.9	7.7	2.7	2.41	0.056	1.7	0.428	1.8	0.08	0.72
30 mg/kg	6	Mean	120.0	55.7	8.0++	17.02	0.568	141.2	4.690	106.0	9.92	7.92
		S.D.	19.8	6.4	2.6	4.33	0.047	1.2	0.333	1.7	0.28	0.75
100 mg/kg	6	Mean	120.0	54.8	9.7+	15.42	0.557	140.5	4.565	105.7	9.87	7.80
		S.D.	14.4	9.6	2.8	3.37	0.028	1.4	0.412	1.5	0.19	0.38
300 mg/kg	6	Mean	134.0	55.3	16.5	15.92	0.562	137.7**	4.703	102.5*	10.03	8.33
		S.D.	27.2	7.9	8.5	3.59	0.050	1.2	0.635	2.2	0.29	1.15

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).
** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).
+ : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Mann-Whitney's U-test).
++ : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Mann-Whitney's U-test).

Table 27 Biochemical findings of male rats in 14-day recovery study following 28-day repeated oral dose of (SR09244)

Group	Number of animals		TP g/dL	Albumin g/dL	A/G ratio	Protein fraction %					AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L	T-Bil mg/dL
						Albumin	Globulin								
							α_1	α_2	β	γ					
0 mg/kg	6	Mean	5.60	2.913	1.088	52.07	20.77	6.87	15.07	5.23	70.7	25.8	520.7	0.68	0.047
		S.D.	0.17	0.104	0.080	1.91	0.94	0.45	0.48	2.01	10.0	3.6	99.5	0.16	0.014
300 mg/kg	6	Mean	5.57	2.855	1.060	51.35	21.92	6.90	14.87	4.97	66.7	25.8	488.7	0.67	0.060
		S.D.	0.19	0.048	0.084	1.89	1.43	0.44	0.67	1.99	15.0	5.8	94.0	0.15	0.009

Group	Number of animals		Glucose mg/dL	T-Cho mg/dL	TG mg/dL	UN mg/dL	Crea mg/dL	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
0 mg/kg	6	Mean	174.0	53.0	47.7	14.57	0.572	142.3	4.540	105.3	9.50	7.40
		S.D.	14.7	10.7	20.0	0.48	0.026	1.4	0.255	1.5	0.26	0.27
300 mg/kg	6	Mean	171.5	65.5*	79.8*	14.85	0.538	141.0	4.955	105.0	9.73	7.65
		S.D.	25.4	4.9	28.6	1.54	0.026	0.6	0.403	0.9	0.12	0.19

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

Table 28 Biochemical findings of female rats in 14-day recovery study following 28-day repeated oral dose of (SR09244)

Group	Number of animals		TP g/dL	Albumin g/dL	A/G ratio	Protein fraction %					AST IU/L	ALT IU/L	ALP IU/L	γ-GTP IU/L	T-Bil mg/dL
						Albumin	Globulin								
							α_1	α_2	β	γ					
0 mg/kg	6	Mean	6.12	3.373	1.230	55.10	19.32	6.28	13.47	5.83	61.7	20.8	237.5	0.73	0.065
		S.D.	0.33	0.205	0.076	1.53	1.38	0.68	0.99	1.00	3.4	3.3	64.8	0.19	0.010
300 mg/kg	6	Mean	6.10	3.318	1.197	54.42	20.05	6.27	13.97	5.30	60.8	23.2	229.7	0.58	0.067
		S.D.	0.24	0.127	0.055	1.12	1.25	0.14	0.98	0.83	7.4	5.0	43.3	0.17	0.019

Group	Number of animals		Glucose mg/dL	T-Cho mg/dL	TG mg/dL	UN mg/dL	Crea mg/dL	Na mEq/L	K mEq/L	Cl mEq/L	Ca mg/dL	IP mg/dL
0 mg/kg	6	Mean	128.3	60.8	18.2	17.55	0.633	141.8	4.597	106.5	9.92	7.03
		S.D.	21.6	10.4	13.8	1.99	0.036	1.2	0.212	1.4	0.30	0.97
300 mg/kg	6	Mean	135.3	78.2**	23.3	18.75	0.680	141.7	4.642	105.8	9.90	7.35
		S.D.	34.4	6.9	16.4	3.23	0.049	1.9	0.187	0.8	0.29	0.92

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

Table 29 Gross findings of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	End of administration				End of recovery	
Group	Control				Control	
Dose (mg/kg)	0	30	100	300	0	300
Number of animals examined	6	6	6	6	6	6
No abnormal findings	6	6	5	6	6	5
Organ : Findings						
Liver : Grayish white patch, lobes	0	0	0	0	0	1
Skin of dorsal retion : Scab, bilateral	0	0	1	0	0	0

Values are expressed as the number of animals.

Table 30 Gross findings of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Period	End of administration				End of recovery	
Group	Control				Control	
Dose (mg/kg)	0	30	100	300	0	300
Number of animals examined	6	6	6	6	6	6
No abnormal findings	6	6	6	5	6	6
Organ : Findings						
Incicor : Fracture, unilateral	0	0	0	1	0	0

Values are expressed as the number of animals.

Table 31 Absolute and relative organ weights of male rats in 28-day repeated dose oral toxicity study of (SR09244)

Group	Number of animals		Body weight g	Liver g	Liver %	Kidney g	Kidney %	Spleen g	Spleen %	Heart g	Heart %	Brain g	Brain %	Pituitary gland mg	Pituitary gland 10^{-3}%
0 mg/kg	6	Mean	334.2	9.878	2.953	2.378	0.712	0.568	0.172	1.107	0.332	2.022	0.607	11.52	3.448
		S.D.	12.5	1.021	0.246	0.139	0.031	0.108	0.034	0.125	0.031	0.055	0.021	0.86	0.258
30 mg/kg	6	Mean	350.8	10.563	3.010	2.448	0.700	0.750*	0.213*	1.065	0.302	2.043	0.582	11.12	3.168
		S.D.	18.7	0.942	0.209	0.228	0.073	0.109	0.023	0.123	0.036	0.196	0.057	1.61	0.425
100 mg/kg	6	Mean	360.2	11.933**	3.317*	2.520	0.698	0.815**	0.225**	1.253	0.347	2.057	0.572	12.42	3.430
		S.D.	23.8	0.901	0.205	0.257	0.032	0.107	0.023	0.147	0.023	0.079	0.035	2.38	0.453
300 mg/kg	6	Mean	343.3	12.133**	3.527**	2.495	0.727	0.830**	0.240**	1.172	0.342	2.128	0.618	12.13	3.528
		S.D.	15.6	1.241	0.223	0.166	0.023	0.109	0.023	0.099	0.015	0.086	0.018	1.40	0.306

Group	Number of animals		Thymus mg	Thymus 10^{-3}%	Thyroid mg	Thyroid 10^{-3}%	Adrenal mg	Adrenal 10^{-3}%	Testis g	Testis %	Epididymis g	Epididymis %	Prostate mg	Prostate 10^{-3}%	Seminal vesicle g	Seminal vesicle %
0 mg/kg	6	Mean	470.7	140.570	17.93	5.367	60.7	18.135	3.067	0.917	0.700	0.210	510.3	153.035	1.178	0.355
		S.D.	76.2	20.533	3.40	0.979	13.4	3.764	0.132	0.044	0.035	0.011	88.2	27.950	0.209	0.073
30 mg/kg	6	Mean	640.7	183.182	20.25	5.758	57.7	16.493	3.078	0.880	0.630	0.180**	444.5	126.932	1.182	0.340
		S.D.	97.6	29.823	5.06	1.301	6.8	2.299	0.174	0.077	0.036	0.006	77.9	22.846	0.152	0.057
100 mg/kg	6	Mean	542.7	150.433	20.03	5.567	58.3	16.168	3.125	0.870	0.710	0.198	452.7	125.662	1.430*	0.398
		S.D.	178.6	45.906	4.64	1.228	9.5	2.114	0.306	0.089	0.075	0.015	70.6	17.459	0.153	0.033
300 mg/kg	6	Mean	536.0	156.100	23.85	6.937*	59.0	17.202	3.060	0.895	0.692	0.202	470.7	137.768	1.318	0.382
		S.D.	40.5	9.178	2.44	0.508	7.9	2.385	0.155	0.073	0.054	0.008	86.4	28.165	0.154	0.042

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).
** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

Table 32 Absolute and relative organ weights of female rats in 28-day repeated dose oral toxicity study of (SR09244)

Group	Number of animals		Body weight	Liver		Kidney		Spleen		Heart		Brain		Pituitary gland	
			g	g	%	g	%	g	%	g	%	g	%	mg	10^{-3}%
0 mg/kg	6	Mean	233.7	7.480	3.197	1.715	0.737	0.485	0.207	0.830	0.355	1.927	0.832	13.50	5.817
		S.D.	27.9	0.987	0.145	0.168	0.070	0.079	0.022	0.099	0.014	0.084	0.095	1.80	0.832
30 mg/kg	6	Mean	198.3*	6.352	3.185	1.547	0.783	0.428	0.217	0.720	0.362	1.930	0.982*	13.15	6.675
		S.D.	22.9	1.085	0.218	0.164	0.039	0.065	0.016	0.109	0.023	0.081	0.099	1.64	0.912
100 mg/kg	6	Mean	223.3	7.002	3.137	1.678	0.750	0.532	0.240	0.738	0.328	1.923	0.867	13.07	5.868
		S.D.	20.8	0.744	0.209	0.208	0.040	0.096	0.036	0.125	0.032	0.093	0.083	1.50	0.691
300 mg/kg	6	Mean	239.5	8.275	3.455	1.695	0.715	0.512	0.212	0.867	0.365	2.017	0.847	14.20	5.950
		S.D.	17.5	0.710	0.121	0.328	0.164	0.115	0.040	0.089	0.036	0.049	0.081	1.08	0.542

Group	Number of animals		Thymus		Thyroid		Adrenal		Ovary		Uterus	
			mg	10^{-3}%	mg	10^{-3}%	mg	10^{-3}%	mg	10^{-3}%	g	%
0 mg/kg	6	Mean	461.7	196.140	16.13	6.925	87.2	37.828	103.5	44.227	0.758	0.313
		S.D.	152.5	50.135	2.88	1.106	14.1	8.402	16.9	4.796	0.417	0.136
30 mg/kg	6	Mean	358.7	179.783	15.65	7.873	74.7	37.898	92.0	46.535	0.587	0.288
		S.D.	83.4	32.373	3.08	1.271	5.4	3.286	12.1	4.797	0.335	0.132
100 mg/kg	6	Mean	470.5	209.792	16.63	7.508	82.5	37.083	103.2	46.558	0.775	0.340
		S.D.	91.8	29.380	2.10	1.287	7.7	3.613	17.2	8.720	0.320	0.127
300 mg/kg	6	Mean	411.2	170.788	19.58	8.120	95.2	40.017	108.8	45.365	0.652	0.272
		S.D.	79.7	26.285	4.41	1.485	4.5	4.821	12.8	3.303	0.228	0.083

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

Table 33 Absolute and relative organ weights of male rats in 14-day recovery study following 28-day repeated oral dose of (SR09244)

Group	Number of animals		Body weight	Liver		Kidney		Spleen		Heart		Brain		Pituitary gland	
			g	g	%	g	%	g	%	g	%	g	%	mg	10^{-3}%
0 mg/kg	6	Mean	420.3	12.278	2.922	2.792	0.667	0.792	0.187	1.197	0.287	2.143	0.512	13.77	3.270
		S.D.	31.3	1.072	0.102	0.193	0.051	0.053	0.015	0.106	0.020	0.103	0.022	2.07	0.415
300 mg/kg	6	Mean	434.2	13.393	3.085*	2.955	0.682	0.795	0.182	1.427**	0.330**	2.122	0.488	14.00	3.225
		S.D.	19.7	0.983	0.132	0.260	0.050	0.062	0.012	0.084	0.023	0.059	0.027	1.47	0.340

Group	Number of animals		Thymus		Thyroid		Adrenal		Testis		Epididymis		Prostate		Seminal vesicle	
			mg	10^{-3}%	mg	10^{-3}%	mg	10^{-3}%	g	%	g	%	mg	10^{-3}%	g	%
0 mg/kg	6	Mean	537.5	128.613	22.68	5.417	73.8	17.570	3.438	0.823	1.092	0.258	712.3	170.107	1.400	0.337
		S.D.	110.9	28.875	1.84	0.546	12.1	2.617	0.192	0.082	0.367	0.084	117.6	28.973	0.237	0.069
300 mg/kg	6	Mean	468.0	107.920	22.58	5.203	64.0	14.708	3.485	0.803	1.030	0.238	684.2	157.507	1.660	0.383
		S.D.	57.5	13.902	2.50	0.562	10.3	2.026	0.222	0.039	0.092	0.016	119.0	26.171	0.215	0.040

* : Significantly different from the 0 mg/kg group at $p \leqq 0.05$ (Dunnett's test).

** : Significantly different from the 0 mg/kg group at $p \leqq 0.01$ (Dunnett's test).

Table 34 Absolute and relative organ weights of female rats in 14-day recovery study following 28-day repeated oral dose of (SR09244)

Group	Number of animals		Body weight	Liver		Kidney		Spleen		Heart		Brain		Pituitary gland	
			g	g	%	g	%	g	%	g	%	g	%	mg	10^{-3}%
0 mg/kg	6	Mean	258.7	7.548	2.922	1.777	0.687	0.538	0.207	0.840	0.325	1.965	0.765	14.77	5.760
		S.D.	24.3	0.611	0.070	0.184	0.034	0.075	0.024	0.084	0.027	0.057	0.058	1.60	0.882
300 mg/kg	6	Mean	278.8	8.463	3.028	1.838	0.660	0.578	0.207	0.848	0.305	1.953	0.705	14.97	5.373
		S.D.	22.9	1.127	0.240	0.196	0.043	0.063	0.020	0.056	0.025	0.045	0.070	1.57	0.441

Group	Number of animals		Thymus		Thyroid		Adrenal		Ovary		Uterus	
			mg	10^{-3}%	mg	10^{-3}%	mg	10^{-3}%	mg	10^{-3}%	g	%
0 mg/kg	6	Mean	440.8	169.655	18.63	7.207	85.3	33.017	104.3	40.428	0.537	0.208
		S.D.	69.4	11.512	3.92	1.380	8.8	1.974	11.2	3.931	0.051	0.027
300 mg/kg	6	Mean	505.2	180.905	19.13	6.863	84.2	30.370	112.0	40.190	0.550	0.198
		S.D.	114.9	39.278	3.13	0.942	8.3	4.162	12.7	3.766	0.083	0.015

Table 35 Histopathological findings of male rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Item	Group	End of administration				End of recovery	
		0 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg	0 mg/kg	300 mg/kg
Number of animals examined		6	6	6	6	6	6
Organ: Findings	Grade						
Lung: Aggregation, macrophage, alveolar	+	0	-	-	2	0	0
Liver: Microgranuloma	+	6	-	-	5	6	6
Fatty change, periportal	+	0	-	-	0	0	1
Heart: Myocardial degeneration, focal	+	0	-	-	1	1	1
Kidney: Hyaline droplet, proximal tubular epithelium	+	1	-	-	0	0	0
Regeneration, tubular epithelium	+	1	-	-	2	0	0
Cellular infiltration, inflammatory cell, cortex	+	1	-	-	1	0	0
Cast, hyaline	+	0	-	-	0	1	0
Cyst	<+>	0	-	-	0	0	1
Prostate: Cellular infiltration, inflammatory cell	+	0	-	-	0	3	1
Spleen: Increase, extramedullary hematopoiesis	+	0	0	0	4	0	0
Pituitary gland: Cyst, pars distalis	<+>	0	-	-	0	1	0
Eyeball: Mineralization, cornea	+	1	-	-	1	1	2
Skin: Ulcer	+	-	-	1 (1)	-	-	-
Scab	+	-	-	1 (1)	-	-	-
Cellular infiltration, inflammatory cell, dermis	+	-	-	1 (1)	-	-	-
Fibrosis, dermis	+	-	-	1 (1)	-	-	-
Edema, dermis	+	-	-	1 (1)	-	-	-

Values are number of animals with findings.
Values in parentheses are number of animals examined.
-: Blank.
Grade; +: slight change, <+>: presence in "presence or not" basis.

Table 36 Histopathological findings of female rats in 28-day repeated dose oral toxicity study and 14-day recovery study of (SR09244)

Item	Group	End of administration				End of recovery	
		0 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg	0 mg/kg	300 mg/kg
Number of animals examined		6	6	6	6	6	6
Organ: Findings	Grade						
Lung: Aggregation, macrophage, alveolar	+	0	-	-	1	0	0
Granuloma, foreign body	+	1	-	-	0	0	0
Liver: Microgranuloma	+	1	-	-	1	0	2
Fatty change, periportal	+	1	-	-	0	1	0
Kidney: Cellular infiltration, inflammatory cell, renal pelvic mucosa	+	1	-	-	0	1	0
Urinary bladder: Cellular infiltration, inflammatory cell, lamina propria	+	1	-	-	0	0	0
Papillary hyperplasia, transitional epithelium	++	1	-	-	0	0	0
Spleen: Increase, extramedullary hematopoiesis	+	0	0	0	1	0	0
Pituitary gland: Cyst, pars nervosa	<+>	0	-	-	0	1	0
Hyperplasia, tubular, pars intermedia	+	0	-	-	0	0	1
Eyeball: Mineralization, cornea	+	2	-	-	2	0	0
Incisor: Gingivitis	++	-	-	-	1 (1)	-	-

Values are number of animals with findings.
Values in parentheses are number of animals examined.
-: Blank.
Grade; +: slight change, ++: moderate change, <+>: presence in "presence or not" basis.